Medical
610.5
R89
v.51
Subject Index to v.45

# PROCEEDINGS

OF THE

# ROYAL SOCIETY OF MEDICINE

EDITED UNDER THE DIRECTION OF THE EDITORIAL COMMITTEE

HONORARY EDITORS: E. C. WARNER, M.D., F.R.C.P., AND SELWYN TAYLOR, M.CH., F.R.C.S.

EDITOR: J. M. BROWNE KUTSCHBACH, M.B., D.P.H.

*VOLUME THE FIFTY-FIRST* *JANUARY TO DECEMBER 1958*

(SESSION OCTOBER 1957—SEPTEMBER 1958)

## SECTIONS

ANÆSTHETICS
CLINICAL
COMPARATIVE MEDICINE
DERMATOLOGY
ENDOCRINOLOGY
EPIDEMIOLOGY AND PREVENTIVE MEDICINE
EXPERIMENTAL MEDICINE AND THERAPEUTICS
GENERAL PRACTICE
HISTORY OF MEDICINE
LARYNGOLOGY
MEDICINE
NEUROLOGY
OBSTETRICS AND GYNÆCOLOGY
ODONTOLOGY
OPHTHALMOLOGY
ORTHOPÆDICS
OTOLOGY
PÆDIATRICS
PATHOLOGY
PHYSICAL MEDICINE
PROCTOLOGY
PSYCHIATRY
RADIOLOGY
SURGERY
UNITED SERVICES
UROLOGY




LONDON
H. K. LEWIS & CO. LTD., 136 GOWER STREET, LONDON, W.C.1
1958

# CONTENTS OF SECTIONS

**PROCEEDINGS VOLUME 51, 1958**


| | PAGE Sect. | Vol. |
|---|---|---|
| **Book Reviews** | | |
| *January No.* | — | 39, 53 |
| *February No.* | — | 133 |
| *March No.* | — | 221 |
| *April No.* | — | 275 |
| *May No.* | — | 371 |
| *June No.* | — | 465 |
| *July No.* | — | 577 |
| *August No.* | — | 687 |
| *September No.* | — | 785 |
| *October No.* | — | 885 |
| *November No.* | — | 973 |
| *December No.* | — | 1061 |
| **Section of Anæsthetics** | | |
| *March No.* Meeting Jan. 3, 1958 | | |
| DISCUSSION ON ORGANIZATION FOR IMMEDIATE POST-OPERATIVE RECOVERY PERIOD | 1 | 151 |
| Dr. Russell M. Davies | 1 | 151 |
| Mr. J. R. Belcher | 3 | 153 |
| Dr. T. B. Boulton | 4 | 154 |
| Dr. A. C. Fraser, Dr. Eric Gardner, Dr. G. F. Rawdon Smith, Dr. J. Alfred Lee, Dr. Laurence Mountford | 5 | 155 |
| Mr. St. John Birt, Professor E. A. Pask, Mr. Belcher, Dr. Davies | 6 | 156 |
| *August No.* Meeting March 7, 1958 | | |
| DISCUSSION ON THE EXTRACORPOREAL CIRCULATION | 7 | 579 |
| Dr. H. C. Churchill-Davidson [*Abridged*] | 7 | 579 |
| Dr. Cyril F. Scurr | 9 | 581 |
| Dr. John Beard | 17 | 589 |
| Dr. W. A. Hudson | 19 | 591 |
| *October No.* Meeting April 11, 1958 | | |
| Meeting to Commemorate the Centenary of the Death of John Snow | | |
| JOHN SNOW'S LONDON ASSOCIATIONS. By George Edwards, L.R.C.P., M.R.C.S. | 21 | 831 |
| JOHN SNOW AND THE ENLIGHTENMENT. By M. H. Armstrong Davison, M.B.E., T.D., M.D. | 24 | 834 |
| **Clinical Section** | | |
| *March No.* Meeting Nov. 8, 1957 | | |
| GUMMATOUS ULCERS WITH GROSS HEPATOMEGALY AND ANÆMIA. By A. B. Wootliff, M.B., Ch.B. (for J. M. Milloy, F.R.C.S.) | 1 | 177 |
| ADDISON'S DISEASE WITH GLYCYRRHIZOPHILIA. By J. P. Knowles, M.B., B.Chir., D.Obst. (for Richard Asher, M.D., F.R.C.P.) | 2 | 178 |
| *March No.* Meeting Dec. 13, 1957 | | |
| PULSELESS DISEASE AND PULMONARY SARCOIDOSIS. By T. M. Chalmers, M.D. | 3 | 179 |
| TRAUMATIC ANEURYSM OF THE POPLITEAL ARTERY IN A BOY AGED 11 YEARS, ASSOCIATED WITH AN OSTEOMA OF THE LOWER FEMUR. TREATMENT BY ANEURYSMECTOMY AND REPAIR OF VESSEL WALL. By A. M. Desmond, F.R.C.S. | 3 | 179 |
| ECTOPIC PHÆOCHROMOCYTOMA. By R. E. Williams, M.R.C.P. (for Professor M. L. Rosenheim, C.B.E., F.R.C.P., B. J. Harries, F.R.C.S., and John Lister, M.D.) | 4 | 180 |
| POSTURAL APHONIA. By A. G. Grant, L.R.C.P.I., L.R.C.S.I. (for F. Boyes Korkis, F.R.C.S.) | 6 | 182 |
| *May No.* Meeting Feb. 14, 1958 | | |
| Meeting at the Middlesex Hospital, London | | |
| HYPOPHYSECTOMY FOR INCIPIENT BLINDNESS DUE TO PROGRESSIVE DIABETIC RETINOPATHY. By J. D. H. Slater, M.B., M.R.C.P. (for J. D. N. Nabarro, M.D., F.R.C.P.) | 7 | 365 |
| SENSORY NERVE CONDUCTION AFTER TRACTION LESION OF THE BRACHIAL PLEXUS. By George Bonney, M.S., F.R.C.S., and R. W. Gilliatt, D.M., M.R.C.P. | 7 | 365 |
| TRAUMATIC, RIGHT-SIDED, DIAPHRAGMATIC HERNIA: A MISTAKE IN DIAGNOSIS. By J. K. Ross, F.R.C.S., and L. P. Le Quesne, D.M., F.R.C.S. | 9 | 367 |
| RENAL TUBERCULOSIS. ILEOCYSTOPLASTY. By E. W. Riches, M.C., M.S., F.R.C.S. | 11 | 369 |
| *August No.* Meeting March 14, 1958 | | |
| CARCINOMA OF PANCREAS. By Paul T. Savage, M.B., F.R.C.S. | 13 | 593 |
| PHÆOCHROMOCYTOMA. By W. W. Davey, M.D., F.R.C.S., F.R.C.S.I. | 14 | 594 |
| TRACHEO-ŒSOPHAGEAL FISTULA WITHOUT ATRESIA. By R. H. Franklin, F.R.C.S. | 15 | 595 |
| *August No.* Meeting May 9, 1958 | | |
| Meeting at the Canadian Red Cross Memorial Hospital, Taplow, Maidenhead | | |
| THE EYE CHANGES OF STILL'S DISEASE: TWO CASES ILLUSTRATING TREATMENT. By W. K. Smiley, M.B., D.O.M.S., F.R.C.S. | 17 | 597 |

| | PAGE Sect. | Vol. |
|---|---|---|
| POLYARTERITIS NODOSA AND HYDRONEPHROSIS. By G. S. Wakefield, M.R.C.P. (for Professor E. G. L. Bywaters, F.R.C.P.), and Raymond Ramsay, M.B.E., F.R.C.S. .. | 18 | 598 |
| ENCEPHALOMYELITIS DUE TO VIRUS B. By Philip H. Willcox, M.D., M.R.C.P. .. .. .. .. | 20 | 600 |

**Section of Comparative Medicine**

*January No.* Meeting Oct. 16, 1957

| | | |
|---|---|---|
| COMPARATIVE ASPECTS IN VIROLOGY. President's Address by J. B. Brooksby, D.Sc., Ph.D., M.R.C.V.S. | 1 | 1 |

*May No.* Meeting Dec. 18, 1957

| | | |
|---|---|---|
| SYMPOSIUM ON RECENT DEVELOPMENTS IN IMMUNIZATION AGAINST BACTERIAL DISEASE .. .. .. | 9 | 375 |
| THE BASIS OF IMMUNITY TO ANTHRAX. By H. Smith, D.Sc., Ph.D., B.Sc... | 9 | 375 |
| STRAIN 19 AND OTHER BRUCELLA VACCINES. By E. C. Hulse, B.Sc., M.R.C.V.S. .. .. .. .. | 11 | 377 |
| IMMUNOLOGICAL RESPONSE TO FREEZE-DRIED BCG. By J. Ungar, M.D... | 14 | 380 |

*July No.* Meeting March 19, 1958

| | | |
|---|---|---|
| DISCUSSION ON COMPARISON OF DISORDERS OF THE INTERVERTEBRAL DISC IN MAN AND ANIMALS .. | 19 | 569 |
| Mr. D. D. Lawson.. .. .. | 19 | 569 |
| Dr. R. N. Smith .. .. .. | 21 | 571 |
| Mr. Arthur Naylor .. .. | 23 | 573 |

*September No.* Meeting Feb. 19, 1958

| | | |
|---|---|---|
| IRRADIATED HELMINTH LARVÆ IN VACCINATION. By W. F. H. Jarrett, Ph.D., M.R.C.V.S., F. W. Jennings, B.Sc., M.Agr., W. I. M. McIntyre, Ph.D., M.R.C.V.S., W. Mulligan, M.Sc., Ph.D., and G. M. Urquhart, Ph.D., M.R.C.V.S... .. .. | 27 | 743 |

**Section of Comparative Medicine with Section of Pathology**

*(JOINT MEETING No. 1)*

*September No.* Meeting April 16, 1958

| | | |
|---|---|---|
| DISCUSSION ON RECENT ADVANCES IN DEMYELINATING DISEASE .. | — | 745 |
| EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS AND ITS IMMUNOCHEMISTRY. By Jack Colover, M.D., M.R.C.P. | — | 745 |
| RECENT ADVANCES IN SWAYBACK. By R. M. Barlow, B.Sc., M.R.C.V.S. | — | 748 |
| DEMYELINATING DISEASE : THE PRESENT SITUATION. By Professor C. E. Lumsden, M.D. .. .. | — | 752 |

**Section of Dermatology**

*March No.* Meeting Oct. 17, 1957

| | | |
|---|---|---|
| CHRONIC GRANULOMA OF FACE. By F. F. Hellier, O.B.E., F.R.C.P. .. | 1 | 173 |
| CHLORACNE. By C. M. Ridley, M.R.C.P. .. .. .. .. | 2 | 174 |
| List of other Cases shown .. .. | 3 | 175 |

*March No.* Meeting Nov. 21, 1957

| | | |
|---|---|---|
| MUCOUS MEMBRANE PEMPHIGOID. By J. H. Allison, M.R.C.P. (for F. Ray Bettley, F.R.C.P.) .. | 3 | 175 |
| PEMPHIGUS VEGETANS. By F. Ray Bettley, F.R.C.P. .. .. .. | 4 | 176 |

*May No.* Meeting Oct. 17, 1957, *contd.*

| | | |
|---|---|---|
| Presidential Address (*By Title*) .. | 5 | 321 |

*May No.* Meeting Nov. 21, 1957, *contd.*

| | | |
|---|---|---|
| SCLEREDEMA [BUSCHKE]. By C. M. Vesey, M.R.C.S., L.R.C.P. (for C. D. Calnan, M.R.C.P.) .. .. | 5 | 321 |
| ŒDEMATOUS SCLERODERMA. By C. D. Calnan, M.R.C.P. .. .. .. | 5 | 321 |
| List of other Cases shown .. .. | 5 | 321 |

*May No.* Meeting Dec. 19, 1957

| | | |
|---|---|---|
| ALOPECIA MUCINOSA (PINKUS). By I. Martin-Scott, M.D. .. .. | 6 | 322 |
| NORMOCHOLESTEROLÆMIC XANTHOMATOSIS. By P. F. Borrie, M.D... | 8 | 324 |
| LIVIDO RETICULARIS. By P. F. Borrie, M.D... .. .. .. .. | 8 | 324 |
| GOUGEROT'S MALADIE TRISYMPTOMATIQUE WITH CRYOGLOBULINÆMIA. By D. C. G. Bett, M.R.C.P. (for Stephen Gold, M.D.) .. .. | 9 | 325 |
| CRYOGLOBULINÆMIA AND RETICULOSIS. By E. N. M. Johnston, M.R.C.P., and H. J. Wallace, M.D., F.R.C.P. | 9 | 325 |
| List of other Cases shown .. .. | 10 | 326 |

*June No.* Meeting Jan. 16, 1958

| | | |
|---|---|---|
| PSORIASIS. By D. I. Williams, F.R.C.P. .. .. .. .. | 11 | 421 |
| RETICULOHISTIOCYTOMA (TYPE CARO/SENEAR). By Denis Sharvill, M.R.C.P. .. .. .. .. | 12 | 422 |
| CUTANEOUS HÆMANGIOMATA AND BONY DEFORMITIES (KLIPPEL-TRENAUNAY and PARKES WEBER SYNDROME). By J. Everall, M.R.C.P., and M. Feiwel, M.R.C.P. (for G. B. Mitchell-Heggs, O.B.E., F.R.C.P.) .. .. .. .. | 13 | 423 |
| List of other Cases shown .. .. | 14 | 424 |

*July No.* Meeting Feb. 20, 1958

| | | |
|---|---|---|
| KAPOSI'S VARICELLIFORM ERUPTION (ECZEMA HERPETICUM) TREATED WITH PREDNISONE. By S. C. Gold, M.D... .. .. .. .. | 15 | 517 |

| | PAGE Sect. | Vol. |
|---|---|---|
| MULTIPLE SKIN NECROSES (ARTERIOLAR)—INGRAM AND SUTHERLAND. By Maurice Garretts, M.B., M.R.C.P. (for W. N. Goldsmith, M.D., F.R.C.P.) .. .. .. | 16 | 518 |
| PRETIBIAL MYXŒDEMA. By K. M. Harvey, M.B. (for Brian F. Russell, M.D., F.R.C.P.) .. .. | 17 | 519 |
| List of other Cases shown .. .. | 18 | 520 |
| *July No.* Meeting March 20, 1958 | | |
| Symposium (*By Title*) .. .. | 18 | 520 |
| List of Cases and Demonstrations .. | 18 | 520 |
| *September No.* Meeting April 17, 1958 | | |
| ANGIOKERATOMA CORPORIS DIFFUSUM. By H. J. Wallace, M.D. | 19 | 707 |
| ECTODERMAL DEFECT WITH SKELETAL ABNORMALITIES. By E. Wilson Jones, M.R.C.P. (for H. J. Wallace, M.D., F.R.C.P.) .. .. .. | 19 | 707 |
| ECZEMA WITH ACANTHOLYTIC BULLÆ. By H. T. H. Wilson, M.R.C.P. .. | 20 | 708 |
| MULTIPLE SEBACEOUS PAPILLOMAS. By P. A. J. Smith, M.B., M.R.C.P. | 21 | 709 |
| GENERALIZED NÆVOID PIGMENTATION. By E. Wilson Jones, M.R.C.P. (for H. J. Wallace, F.R.C.P., and R. J. Cairns, M.R.C.P.) .. .. .. | 22 | 710 |
| ONYCHOLYSIS FROM ADHESIVES. By G. C. Wells, M.R.C.P. .. .. | 23 | 711 |
| CALCINOSIS. By E. N. M. Johnston, M.R.C.P. .. .. .. .. | 23 | 711 |
| LICHEN NITIDUS. By H. T. H. Wilson, M.R.C.P. .. .. .. .. | 24 | 712 |
| *November No.* Meeting April 17, 1958, *contd.* | | |
| List of Cases shown .. .. .. | 25 | 929 |
| *November No.* Meeting May 15, 1958 | | |
| LUPOID ROSACEA. By Brian F. Russell, F.R.C.P. .. .. .. .. | 25 | 929 |
| TUBERCULOSIS VERRUCOSA CUTIS (? WATERBORNE ACID-FAST BACILLUS INFECTION). By J. S. Pegum, M.D. | 26 | 930 |
| EOSINOPHILIC GRANULOMA OF THE FACE OF THE ERYTHEMA ELEVATUM DIUTINUM TYPE. By I. Sarkany, M.R.C.P. (for Louis Forman, M.D., F.R.C.P.) .. .. .. | 26 | 930 |
| List of other Cases shown .. .. | 27 | 931 |
| *November No.* Meeting June 7, 1958 | | |
| Meeting at the General Infirmary, Leeds | | |
| MADURA FOOT (MYCETOMA). By S. T. Anning, M.D., F.R.C.P. .. | 27 | 931 |
| LYMPHOCYTIC LYMPHOMA. By J. T. Ingram, M.D., F.R.C.P. .. .. | 27 | 931 |
| ELASTOMA INTRAPAPILLARE PERFORANS VERRUCIFORME (MIESCHER). By S. T. Anning, M.D., F.R.C.P. | 28 | 932 |
| LUPUS ERYTHEMATOSUS (PROFUNDUS). By J. T. Ingram, M.D., F.R.C.P. | 28 | 932 |
| CASE FOR DIAGNOSIS. ? POIKILODERMA IN A BABY. By F. F. Hellier, O.B.E., F.R.C.P. .. .. .. | 28 | 932 |
| POIKILODERMA AND PIGMENTED LICHEN SCLEROSUS (LUPUS ERYTHEMATOSUS). By J. T. Ingram, M.D., F.R.C.P. .. .. .. | 29 | 933 |
| List of other Cases shown .. .. | 29 | 933 |
| *November No.* Meeting June 26, 1958 | | |
| POLYMYOSITIS AND THYROIDITIS. By Denis Sharvill, M.R.C.P. .. .. | 30 | 934 |
| SCLERODERMA AND CARCINOMA. By Louis Forman, M.D., F.R.C.P., and Hedley Atkins, M.Ch. .. | 31 | 935 |
| BESNIER'S PRURIGO WITH CALCINOSIS. By Brian Russell, M.D., F.R.C.P. | 31 | 935 |
| List of other Cases shown .. .. | 32 | 936 |
| **Section of Endocrinology** | | |
| *January No.* Meeting Oct. 23, 1957 | | |
| THE CLINICAL DIAGNOSIS OF SEX. President's Address by C. N. Armstrong, M.D., F.R.C.P. .. | 1 | 23 |
| *March No.* Meeting July 24, 1957 | | |
| THE PHYSIOLOGICAL CONTROL OF ALDOSTERONE SECRETION [*Abridged*]. By Frederic C. Bartter, M.D. .. .. .. .. | 5 | 201 |
| *March No.* Meeting Nov. 27, 1957 | | |
| IDIOPATHIC HYPOPARATHYROIDISM WITH THIN BONES. By H. K. Ibbertson, M.R.C.P., M.R.A.C.P., and Russell Fraser, M.D., F.R.C.P. | 6 | 202 |
| PRE-TIBIAL MYXŒDEMA FOLLOWING SUBTOTAL THYROIDECTOMY AND RECURRING AFTER SURGICAL EXCISION. By J. H. Briggs, M.B. (for P. M. F. Bishop, D.M.) .. .. | 8 | 204 |
| List of other Cases shown .. .. | 8 | 204 |
| *May No.* Meeting Jan. 22, 1958 | | |
| DISCUSSION ON ENDOCRINE CHANGES IN LIVER DISEASE .. .. .. | 9 | 359 |
| Dr. Sheila Sherlock .. .. | 9 | 359 |
| Dr. J. Lee and Dr. G. W. Bisset .. | 11 | 361 |
| Dr. W. H. J. Summerskill .. .. | 13 | 363 |
| *July No.* Meeting Feb. 26, 1958 | | |
| SOME OBSERVATIONS ON THE MECHANISM OF INSULIN ACTION IN MUSCLE. By P. J. Randle, M.A., Ph.D., M.B., B.Chir., and G. Howard Smith, M.A., B.Sc., Ph.D. | 15 | 551 |

| | PAGE Sect. | Vol. |
|---|---|---|
| CORTICOTROPHIN TESTS IN HIRSUTE WOMEN. By J. D. N. Nabarro, M.D., F.R.C.P., Audrey Moxham, J. D. H. Slater, M.B., M.R.C.P., and G. Walker, M.B., M.R.C.P.. . | 16 | 552 |
| THE IMPORTANCE OF DIFFERENTIAL ASSAY OF URINARY FSH AND ICSH. By P. S. Brown, B.M., M.R.C.P. .. .. .. .. | 18 | 554 |
| *July No.* Meeting March 26, 1958 | | |
| THE URINARY EXCRETION OF ŒSTROGENS, PREGNANEDIOL AND PITUITARY GONADOTROPHINS DURING THE MENSTRUAL CYCLE [*Abridged*]. By J. B. Brown, M.Sc., Ph.D., A. I. Klopper, B.Sc., Ph.D., M.B., M.R.C.O.G., and J. A. Loraine, M.B., Ph.D., M.R.C.P.(Ed.) .. | 20 | 556 |
| SOME EFFECTS OF 17α-ETHYL-19-NORTESTOSTERONE IN MAN. By F. T. G. Prunty, M.D., F.R.C.P., R. V. Brooks, Ph.D., Barbara E. Clayton, M.D., Ph.D., and R. R. McSwiney, M.B. .. .. .. | 21 | 557 |
| SOME OBSERVATIONS ON ADRENOCORTICOTROPHIN IN BLOOD. By Barbara E. Clayton, M.D., Ph.D. | 22 | 558 |
| THE NEURAL INTERMEDIATE LOBE HORMONE ("B"). By F. W. Landgrebe, D.Sc., and G. M. Mitchell, M.B. .. .. .. | 24 | 560 |
| *September No.* Meeting April 23, 1958 | | |
| CROHN'S DISEASE WITH FEATURES SUGGESTING ADDISON'S DISEASE. By D. Mattingly, M.B., M.R.C.P. (for Professor F. T. G. Prunty, M.D., F.R.C.P.) .. .. .. | 27 | 719 |
| CONN'S SYNDROME. By P. K. M. Barrett, M.B., R. I. S. Bayliss, M.D., F.R.C.P., and J. R. Rees, M.B., M.R.C.P. .. .. .. | 28 | 720 |
| CŒLIAC DWARFISM, WITH ANÆMIA and OSTEOMALACIA. By O. Garrod, M.D. .. .. .. .. | 30 | 722 |
| FEMALE PSEUDOHERMAPHRODITISM. By H. K. Ibbertson, M.R.C.P., M.R.A.C.P., and Russell Fraser, M.D., F.R.C.P. .. .. .. | 31 | 723 |
| *September No.* Meeting May 28, 1958 | | |
| Discussion (*By Title*) .. .. .. | 32 | 724 |
| *December No.* Meeting Oct. 22, 1958 | | |
| THE INTERPRETATION OF HORMONAL ABNORMALITIES. President's Address by Professor F. T. G. Prunty, M.D., F.R.C.P. .. .. .. | 33 | 1073 |


## Section of Epidemiology and Preventive Medicine


| | PAGE Sect. | Vol. |
|---|---|---|
| *March No.* Meeting Oct. 18, 1957 | | |
| SYMPOSIUM ON OPERATIONAL RESEARCH IN THE NATIONAL HEALTH SERVICE .. .. .. .. | 1 | 139 |
| Dr. J. N. Morris .. .. .. | 1 | 139 |
| Dr. J. A. H. Lee, Dr. F. M. Martin | 2 | 140 |
| Mr. Louis Moss .. .. .. | 4 | 142 |
| *March No.* Meeting Nov. 15, 1957 | | |
| SYMPOSIUM ON EVENTS IN PREGNANCY IN RELATION TO DISEASE AND DEFECTS IN THE INFANT .. .. | 8 | 146 |
| Dr. Alison D. McDonald .. | 8 | 146 |
| Dr. R. G. Record .. .. .. | 9 | 147 |
| Dr. J. A. McCredie Smith .. | 11 | 149 |
| *April No.* Meeting Jan. 17, 1958 | | |
| SYMPOSIUM ON WEATHER AND DISEASE | 13 | 259 |
| Mr. R. G. Veryard.. .. .. | 13 | 259 |
| Mr. E. N. Lawrence .. .. | 15 | 261 |
| Dr. P. J. Lawther .. .. .. | 16 | 262 |
| Dr. B. B. Waddy .. .. .. | 18 | 264 |
| *October No.* Meeting Feb. 21, 1958 | | |
| SYMPOSIUM ON EPIDEMIOLOGICAL RISKS OF ANTIBIOTICS .. .. | 21 | 807 |
| Dr. E. J. L. Lowbury .. .. | 21 | 807 |
| Dr. J. B. Selkon .. .. .. | 24 | 810 |
| Dr. H. Williams Smith .. .. | 26 | 812 |
| *December No.* Meeting May 16, 1958 | | |
| Joint Meeting with the Fever Group of the Society of Medical Officers of Health | | |
| SYMPOSIUM ON THE ASIAN INFLUENZA EPIDEMIC, 1957 .. .. .. | 29 | 1009 |
| Dr. A. M.-M. Payne .. .. | 29 | 1009 |
| Dr. J. C. McDonald .. .. | 36 | 1016 |


## Section of Experimental Medicine and Therapeutics


| | PAGE Sect. | Vol. |
|---|---|---|
| *February No.* Meeting Oct. 8, 1957 | | |
| METHODS OF MEASURING PULMONARY DIFFUSING CAPACITY AND THEIR SIGNIFICANCE. By Robert Marshall, M.D., M.R.C.P. .. .. .. | 1 | 101 |
| OLIGOPNŒA [*Abridged*]. By P. Hugh-Jones, M.A., M.D., M.R.C.P. .. | 4 | 104 |
| MECHANISMS OF AIRWAY OBSTRUCTION IN EMPHYSEMA AND ASTHMA. By E. J. M. Campbell, M.D., Ph.D., M.R.C.P. .. .. .. .. | 8 | 108 |
| *June No.* Meeting Dec. 10, 1957 | | |
| GASTRIC FUNCTION .. .. .. | 11 | 461 |
| THE RATE OF GASTRIC EMPTYING IN PATIENTS WITH DUODENAL ULCER. By J. N. Hunt, M.D., D.Sc. .. | 11 | 461 |

| | PAGE Sect. | Vol. |
|---|---|---|
| I. Observations on the Cardiac and Pyloric Sphincters in Man. By M. Atkinson, M.D., M.R.C.P., D. A. W. Edwards, M.D., M.R.C.P., A. J. Honour, and E. N. Rowlands, M.D., F.R.C.P. .. .. .. | 12 | 462 |
| II. Mechanisms of Gastro-œsophageal Reflux in Hiatus Hernia. By M. Atkinson, M.D., M.R.C.P., D. A. W. Edwards, M.D., M.R.C.P., A. J. Honour, and E. N. Rowlands, M.D., F.R.C.P. .. .. .. | 13 | 463 |
| The Gastric Mucosa in Hypochromic Anæmia. By N. F. Coghill, M.A., M.B., M.R.C.P., and A. Wynn Williams, M.D., D.C.P.Lond. .. .. .. | 14 | 464 |
| *August No.* Meeting Feb. 5, 1958 | | |
| Symposium on Hæmoglobin .. | 15 | 639 |
| Professor C. Rimington .. .. | 15 | 639 |
| Dr. A. C. Allison .. .. .. | 17 | 641 |
| Dr. V. M. Ingram .. .. | 21 | 645 |
| Dr. J. H. Walters .. .. .. | 22 | 646 |
| *September No.* Meeting March 11, 1958 | | |
| Acquired Hæmolytic Anæmia. President's Address by Professor J. V. Dacie, M.D., F.R.C.P. .. .. | 25 | 699 |
| **Section of Experimental Medicine and Therapeutics with Section of Neurology** (*JOINT MEETING No.* 2) | | |
| *December No.* Meeting May 13, 1958 | | |
| Discussion on Tetanus .. .. | — | 997 |
| Professor G. Payling Wright .. | — | 997 |
| Dr. D. R. Laurence .. .. | — | 1000 |
| Professor E. B. Adams .. .. | — | 1002 |
| Dr. A. Crampton Smith .. .. | — | 1006 |
| **Section of General Practice** | | |
| *February No.* Meeting Nov. 20, 1957 | | |
| Discussion: The Management of the Hopeless Case .. .. | 1 | 111 |
| Dr. Ronald Gibson .. .. | 1 | 111 |
| Dr. C. J. Gavey .. .. .. | 6 | 116 |
| *April No.* Meeting Jan. 15, 1958 | | |
| Discussion on the Common Cold | 9 | 267 |
| Dr. R. E. Hope Simpson .. .. | 9 | 267 |
| Dr. A. T. Roden .. .. .. | 13 | 271 |
| Dr. J. Morrison Ritchie .. .. | 15 | 273 |
| *May No.* Meeting Dec. 18, 1957 | | |
| Discussion on the Breast in Pregnancy and Lactation .. .. | 17 | 305 |
| Dr. J. C. T. Sanctuary .. .. | 17 | 305 |
| Dr. Mavis Gunther .. .. | 18 | 306 |
| Dr. David Morris .. .. .. | 21 | 309 |
| Dr. Joan Ferreira .. .. .. | 22 | 310 |
| *June No.* Meeting Feb. 19, 1958 | | |
| Discussion on Emergencies in General Practice .. .. | 25 | 441 |
| Dr. R. M. McGregor .. .. | 25 | 441 |
| Dr. J. Guy Ollerenshaw .. .. | 27 | 443 |
| *July No.* Meeting March 19, 1958 | | |
| Discussion: An Appraisal of Hypnotism in General Practice | 31 | 563 |
| Dr. H. Stewart .. .. .. | 31 | 563 |
| Dr. A. A. Mason .. .. .. | 32 | 564 |
| Dr. C. A. H. Watts .. .. | 35 | 567 |
| *August No.* Meeting April 16, 1958 | | |
| Discussion on Management of Practice .. .. .. | 37 | 667 |
| Dr. H. G. Barnes .. .. .. | 37 | 667 |
| Dr. W. F. Hudson .. .. .. | 38 | 668 |
| Dr. J. D. Huntley .. .. .. | 40 | 670 |
| Dr. P. M. Higgins .. .. .. | 42 | 672 |
| Dr. P. A. Walford .. .. .. | 44 | 674 |
| Dr. Stephen Taylor .. .. | 45 | 675 |
| **Section of the History of Medicine** | | |
| *January No.* Meeting Oct. 2, 1957 | | |
| Julius Cæsar and the Falling Sickness. By Terence Cawthorne, F.R.C.S. .. .. .. .. | 1 | 27 |
| *February No.* Meeting Nov. 6, 1957 | | |
| Thudichum and the Medical Chemistry of the 1860s to 1880s. By Henry McIlwain, D.Sc. .. | 5 | 127 |
| *June No.* Meeting Feb. 5, 1958 | | |
| Preventive and Curative Medicine in Ancient Peru [*Abridged*]. President's Address by Sir Weldon Dalrymple-Champneys, Bt., C.B., M.A., D.M., F.R.C.P. .. .. | 11 | 385 |
| *August No.* Meeting May 7, 1958 | | |
| Alexander Pope: Poet and Cripple, 1688–1744. By Sir Arthur Salusbury MacNalty, K.C.B., M.A., M.D. Oxon, F.R.C.P., F.R.C.S. .. .. | 21 | 601 |
| John Arbuthnot, M.D., F.R.C.P., 1667–1735. By W. R. LeFanu, M.A. | 25 | 605 |
| *December No.* Meeting Oct. 1, 1958 | | |
| A Manuscript of Benjamin Collins Brodie's Surgical Lectures, 1822; with Some Notes on the History of Stricture and Stone. By Sir Eric Riches, M.C., M.S., F.R.C.S. | 27 | 1049 |
| **Section of Laryngology** | | |
| *March No.* Meeting Nov. 1, 1957 | | |
| Laryngology—A Retrospect, a Review and a Revaluation. President's Address by R. J. Cann, M.S., F.R.C.S. .. .. .. .. | 1 | 205 |

| | PAGE Sect. | Vol. |
|---|---|---|
| *March No.* Meeting Dec. 6, 1957 | | |
| Discussion (*By Title*) .. .. .. | 4 | 208 |
| *July No.* Meeting Feb. 7, 1958 | | |
| DISCUSSION ON VIRUS INFECTIONS OF THE UPPER RESPIRATORY TRACT .. | 5 | 469 |
| Dr. C. H. Andrewes .. .. | 5 | 469 |
| Professor C. H. Stuart-Harris .. | 7 | 471 |
| Mr. J. Angell James .. .. | 9 | 473 |
| Mr. Ronald Macbeth, Mr. S. W. Allinson, Dr. C. H. Andrewes, Professor C. H. Stuart-Harris .. | 10 | 474 |
| *July No.* Meeting March 7, 1958 | | |
| Papers read (*By Title*) .. .. | 10 | 474 |
| *December No.* Meeting May 2, 1958 | | |
| A POSSIBLE RELATIONSHIP BETWEEN THE SINUSES AND THE LYMPHOID TISSUE OF THE NASOPHARYNX. By A. J. Moffett, T.D., F.R.C.S. .. | 11 | 991 |
| **Section of Laryngology with Section of Otology** | | |
| Joint Summer Meeting held at the Royal College of Surgeons of Edinburgh | | |
| OTOLOGICAL SESSION | | |
| *November No.* Meeting June 27, 1958 | | |
| DISCUSSION ON ACOUSTIC NEUROMA | — | 889 |
| Dr. M. R. Dix and Dr. C. S. Hallpike | — | 889 |
| Professor Norman M. Dott .. | — | 897 |
| Mr. William McKenzie .. .. | — | 898 |
| Dr. Dix, Mr. T. A. Clarke, Mr. I. B. Thorburn, Professor Dott, Dr. J. D. Hood .. .. .. | — | 899 |
| FACIAL PARALYSIS—RESTITUTION BY EXTRA-PETROUS NERVE GRAFT. By Professor Norman M. Dott, C.B.E., F.R.C.S.Ed. .. .. .. .. | — | 900 |
| LARYNGOLOGICAL SESSION | | |
| *December No.* Meeting June 28, 1958 | | |
| Discussion and Paper (*By Title*) .. | | 902 |
| **Section of Medicine** | | |
| *March No.* Meeting Nov. 26, 1957 | | |
| DISCUSSION: INTRACRANIAL HÆMORRHAGE—DIAGNOSIS AND TREATMENT .. .. .. .. .. | 1 | 209 |
| Dr. P. D. Bedford .. .. .. | 1 | 209 |
| Dr. Reginald Kelly .. .. | 5 | 213 |
| Mr. Lawrence S. Walsh .. .. | 9 | 217 |
| *May No.* Meeting Jan. 28, 1958 | | |
| DISCUSSION ON SEDATION AND STIMULATION OF MAN .. .. .. | 13 | 353 |
| Dr. William Sargant .. .. | 13 | 353 |
| Professor E. J. Wayne .. .. | 16 | 356 |
| *July No.* Meeting Feb. 25, 1958 | | |
| DISCUSSION ON SKELETAL MANIFESTATIONS OF GENERAL DISEASE .. | 19 | 475 |
| Dr. Douglas Hubble .. .. | 19 | 475 |
| Dr. R. E. Steiner .. .. .. | 23 | 479 |
| Dr. H. A. Sissons .. .. .. | 29 | 485 |
| Dr. C. E. Dent, Miss Christine M. Harper .. .. .. .. | 33 | 489 |
| *August No.* Meeting March 25, 1958 | | |
| DISCUSSION ON THE LUNGS AS AN INDEX OF SYSTEMIC DISEASE [*Abridged*] .. .. .. .. | 35 | 649 |
| Dr. J. G. Scadding .. .. | 35 | 649 |
| Dr. Philip Ellman .. .. .. | 40 | 654 |
| Dr. A. G. Heppleston .. .. | 47 | 661 |
| *October No.* Meeting May 20, 1958 | | |
| DISCUSSION ON CLINICAL AND LABORATORY ASSESSMENT OF WATER AND ELECTROLYTE DISTURBANCES .. .. .. .. | 53 | 797 |
| Dr. D. A. K. Black .. .. | 53 | 797 |
| Professor G. M. Bull .. .. | 55 | 799 |
| Dr. J. F. Goodwin .. .. .. | 57 | 801 |
| *December No.* Meeting Oct. 28, 1958 | | |
| THE DEVELOPMENT OF THE TREATMENT OF DUODENAL ULCER [*Abridged*]. President's Address by A. H. Douthwaite, M.D., F.R.C.P. .. | 63 | 1063 |
| **Section of Neurology** | | |
| *January No.* Meeting Oct. 3, 1957 | | |
| THE PHYSIOLOGY OF MEMORY. President's Address by W. Ritchie Russell, C.B.E., M.D., D.Sc., F.R.C.P. .. .. .. .. | 1 | 9 |
| *January No.* Meeting Nov. 7, 1957 | | |
| Meeting at the National Hospital for Nervous Diseases, Queen Square, London | | |
| List of Cases shown .. .. .. | 8 | 16 |
| *March No.* Meeting Dec. 5, 1957 | | |
| THE ÆTIOLOGY OF POLYNEURITIS. By A. M. G. Campbell, D.M., F.R.C.P. | 9 | 157 |
| SOME ASPECTS OF REFERRED PAIN [*Abstract*]. By C. W. M. Whitty, D.M., M.R.C.P. .. .. .. | 11 | 159 |
| LATE INFANTILE METACHROMATIC LEUCODYSTROPHY. By Michael Jefferson, D.M., M.R.C.P. .. | 12 | 160 |
| *July No.* Meeting Jan. 2, 1958 | | |
| CHRONIC BENIGN TRIGEMINAL PARESIS. By Professor Brodie Hughes, F.R.C.S. .. .. .. .. | 15 | 529 |
| THE CENTRAL CONTROL OF SENSORY INFLOW. By G. D. Dawson, M.Sc., M.B., Ch.B. .. .. .. .. | 17 | 531 |

| | PAGE Sect. | Vol. |
|---|---|---|
| A Form of Subacute Encephalopathy of Uncertain Ætiology. By S. Nevin, M.D., F.R.C.P., and W. H. McMenemey, M.D., F.R.C.P. | 21 | 535 |
| *July No.* Meeting March 6, 1958 | | |
| Discussion on Vascular Disease of the Spinal Cord | 26 | 540 |
| Dr. D. H. M. Woollam and Dr. J. W. Millen | 26 | 540 |
| Dr. W. Blackwood | 29 | 543 |
| Mr. Joe Pennybacker | 33 | 547 |
| *August No.* Meeting Feb. 6, 1958 | | |
| Discussion on Surgery of Temporal Lobe Epilepsy | 37 | 607 |
| Mr. D. W. C. Northfield | 37 | 607 |
| Dr. Denis Hill | 40 | 610 |
| Mr. Murray A. Falconer | 43 | 613 |
| *October No.* Meeting March 27, 1958 | | |
| Discussion on Some Clinical, Genetic and Biochemical Aspects of Metabolic Disorders of the Nervous System | 47 | 859 |
| Dr. W. B. Matthews | 47 | 859 |
| Dr. R. T. C. Pratt (*By Title*) | 51 | 863 |
| *October No.* Meeting June 27 and 28, 1958 | | |
| Meeting in Oxford with the Roumanian Neurologists | | |
| Programme. Papers (*By Title*) | 52 | 864 |
| *December No.* Meeting Oct. 2, 1958 | | |
| Endogenous Hypoglycæmia. President's Address by Hugh Garland, T.D., M.D., F.R.C.P. | 53 | 979 |
| **Section of Experimental Medicine and Therapeutics with Section of Neurology** (*JOINT MEETING No.* 2) | | |
| *December No.* Meeting May 13, 1958 | | |
| Discussion on Tetanus | — | 997 |
| Professor G. Payling Wright | — | 997 |
| Dr. D. R. Laurence | — | 1000 |
| Professor E. B. Adams | — | 1002 |
| Dr. A. Crampton Smith | — | 1006 |
| **Section of Obstetrics and Gynæcology** | | |
| *March No.* Meeting Nov. 22, 1957 | | |
| Discussion: The Breech | 1 | 163 |
| Dr. G. F. Abercrombie | 1 | 163 |
| Mr. John Hamilton | 2 | 164 |
| Mr. J. H. Peel | 4 | 166 |
| Mr. David Methuen | 7 | 169 |
| Mr. C. K. Vartan | 8 | 170 |
| Mr. Gilbert Dalley, Mr. J. S. Hesketh, Mr. Wilfrid G. Mills | 9 | 171 |
| Dr. J. Vincent O'Sullivan, Mr. John Hamilton | 10 | 172 |
| *March No.* Meeting Jan. 24, 1958 | | |
| List of Cases and Specimens shown | 10 | 172 |
| *June No.* Meeting Feb. 28, 1958 | | |
| Discussion: Early Diagnosis and Cancer Education of the Public | 11 | 403 |
| Mr. Malcolm Donaldson [*Abstract*] | 11 | 403 |
| Dr. John Burton | 12 | 404 |
| Mr. C. J. Thurgar | 13 | 405 |
| Mr. John Wakefield | 14 | 406 |
| Dr. E. V. Kuenssberg | 15 | 407 |
| Mr. Linton Snaith | 16 | 408 |
| *July No.* Meeting March 28, 1958 | | |
| Culdoscopy. By T. N. A. Jeffcoate, M.D., F.R.C.S.Ed., F.R.C.O.G. | 17 | 509 |
| Amnion Nodosum. By J. S. Scott, M.B., M.R.C.O.G., and A. D. Bain, M.D. | 20 | 512 |
| Pregnancy in Addison's Disease. By H. H. Francis, F.R.C.S., M.R.C.O.G., and J. E. Forster, M.B., M.R.C.P. | 21 | 513 |
| *October No.* Meeting April 25, 1958 | | |
| An Obstetrical Forceps Using a New Principle of Parallelism. By Wallace B. Shute, B.A., M.D., M.R.C.O.G., F.R.C.S.(C.) | 25 | 837 |
| List of Specimens shown | 27 | 839 |
| *October No.* Meeting May 30, 1958 | | |
| Discussion on Neonatal Deaths | 28 | 840 |
| Dr. G. R. Osborn | 28 | 840 |
| Dr. A. E. Claireaux | 39 | 851 |
| Dr. Jean M. Smellie | 44 | 856 |
| *October No.* Meeting July 15, 1958 | | |
| Special Meeting (*By Title*) | 46 | 858 |
| **Section of Odontology** | | |
| *January No.* Meeting Feb. 27, 1957, *contd.* | | |
| A New Method of Demonstrating the Retention of Foodstuffs in the Mouth, with Special Reference to Different Forms of Sweets. By Alexander B. MacGregor, M.A., M.D., B.Chir., M.R.C.S., L.R.C.P., F.D.S. R.C.S. | 1 | 41 |
| *April No.* Meeting Oct. 28, 1957 | | |
| Some Observations on Costen's Mandibular Syndrome: Including a Review of 100 out of 500 Cases. President's Address by George T. Hankey, O.B.E., T.D., F.D.S., M.R.C.S., L.R.C.P. | 5 | 225 |

| | PAGE Sect. | Vol. |
|---|---|---|
| *August No.* Meeting Nov. 25, 1957 | | |
| THE SURGICAL AND PROSTHETIC IMPORTANCE OF THE LABIAL AND BUCCAL VESTIBULE OF THE MAXILLÆ [*Abstract*]. By J. H. Lee, L.D.S. R.C.S., and D. Downton, F.D.S. R.C.S. .. .. .. | 13 | 677 |
| *August No.* Meeting Jan. 27, 1958 | | |
| AN EXPERIMENTAL INVESTIGATION INTO THE PERMEABILITY OF ENAMEL AND DENTINE WITH REFERENCE TO ITS RELATION TO DENTAL CARIES. By G. C. Blake, M.B., B.S., F.D.S. | 14 | 678 |
| *September No.* Meeting Feb. 24, 1958 | | |
| TWO CASES OF UNILATERAL HYPERPLASIA OF THE MANDIBULAR CONDYLE. By R. T. Broadway, M.D.S., F.D.S., D.Orth. R.C.S. .. .. | 23 | 691 |
| BILATERAL ANKYLOSIS OF THE TEMPOROMANDIBULAR JOINTS FOLLOWING RHEUMATOID ARTHRITIS. By H. P. Cook, M.B., B.S., B.D.S., F.D.S. R.C.S. .. .. .. | 26 | 694 |
| MELANOMA OF THE HARD PALATE. By G. S. Hoggins, B.D.S., F.D.S. R.C.S., and K. R. Thornton, B.Sc., M.B. .. .. .. .. | 28 | 696 |
| MALIGNANT MELANOMA OF THE HARD AND SOFT PALATE. By W. B. Hales, T.D., F.D.S. R.C.S. .. | 30 | 698 |
| *November No.* Meeting March 24, 1958 | | |
| SOME ABNORMALITIES IN THE NERVE SUPPLY OF THE ORAL MUCOSA. By E. A. Marsland, Ph.D., B.D.S., L.D.S.Eng., and E. C. Fox, M.D., L.D.S.Edin. .. .. .. | 31 | 951 |
| *December No.* Meeting April 28, 1958 | | |
| RESEARCH, ORGANIZATION AND TEACHING IN FORENSIC ODONTOLOGY. By Gösta Gustafson, Dr. odont., F.D.S. R.C.S.Ed. .. | 37 | 1055 |
| THE ASSESSMENT OF AGE FROM THE DENTITION. By A. E. W. Miles, F.D.S., L.R.C.P., M.R.C.S. .. | 39 | 1057 |

## Section of Ophthalmology

| | PAGE Sect. | Vol. |
|---|---|---|
| *January No.* Meeting Oct. 10, 1957 | | |
| THE AGEING EYE. President's Address by J. R. Wheeler, F.R.C.S.Ed. .. | 1 | 17 |
| *June No.* Meeting Feb. 13, 1958 | | |
| FUNCTIONAL SPASM OF ACCOMMODATION [*Summary*]. By L. H. Savin, M.D., M.S., M.R.C.P., F.R.C.S.. . | 7 | 455 |
| THE USE OF PILOCARPINE IN THE TREATMENT OF SQUINTS. By John Whitwell, F.R.C.S., D.O. .. .. | 7 | 455 |
| ORTHOPTIC TREATMENT OF ACCOMMODATIVE CONVERGENT STRABISMUS. By Sheila Mayou, D.B.O.(T.) .. | 9 | 457 |
| *November No.* Meeting March 13, 1958 | | |
| THE CLINICAL FEATURES OF VIRAL KERATITIS AND A CONCEPT OF THEIR PATHOGENESIS. By Barrie R. Jones, F.R.C.S. .. .. .. .. | 13 | 917 |
| *November No.* Meeting June 12, 1958 | | |
| DISCUSSION ON ERYSIPHAKE EXTRACTION OF CATARACT.. .. .. | 20 | 924 |
| Mr. E. C. Zorab .. .. .. | 20 | 924 |
| Mr. J. E. H. Cogan .. .. | 23 | 927 |

## Section of Orthopædics

| | PAGE Sect. | Vol. |
|---|---|---|
| *April No.* Meeting Oct. 1, 1957 | | |
| List of Cases shown .. .. .. | 1 | 233 |
| *April No.* Meeting Nov. 5, 1957 | | |
| TENDON TRANSPLANTS IN POLIOMYELITIS AND IN OBSTETRICAL PALSY [*Summary*]. By Joseph Barr, M.D. | 2 | 234 |
| *April No.* Meeting Dec. 3, 1957 | | |
| SYMPOSIUM ON THE TREATMENT OF ORGANIC SPINAL DEFORMITIES .. | 4 | 236 |
| Mr. J. I. P. James .. .. | 4 | 236 |
| Mr. Robert Roaf .. .. .. | 5 | 237 |
| Mr. Denis Browne .. .. | 8 | 240 |
| *June No.* Meeting Feb. 4, 1958 .. | | |
| RECURRENT SYNOVITIS OF THE KNEE. By Peter R. French, F.R.C.S. .. | 9 | 433 |
| ARTHRODESIS OF THE GREAT TOE. By A. C. Bingold, M.B., F.R.C.S. .. | 11 | 435 |
| ABDUCTION OSTEOTOMY AS A SALVAGE OPERATION IN FRACTURE OF THE NECK OF THE FEMUR. By A. J. Harrold, F.R.C.S. .. .. .. | 14 | 438 |
| ARTERIAL HOMOGRAFTS IN INJURIES OF THE EXTREMITIES. By Jörg Böhler, M.D. .. .. .. | 15 | 439 |
| *October No.* Meeting March 22, 1958 | | |
| Meeting at the Norfolk and Norwich Hospital, Norwich | | |
| SUDECK'S ATROPHY AND THE SHOULDER-HAND SYNDROME. By J. G. Taylor, F.R.C.S. .. .. | 17 | 879 |
| FOUR DEMONSTRATIONS by R. C. Howard, F.R.C.S.Ed. .. .. | 21 | 883 |
| TWO DEMONSTRATIONS by G. K. McKee, F.R.C.S. .. .. .. | 21 | 883 |
| *November No.* Meeting April 1, 1958 | | |
| HALLUX VALGUS IN ADOLESCENTS. President's Address by J. A. Cholmeley, F.R.C.S. .. .. | 23 | 903 |

| | PAGE Sect. | Vol. |
|---|---|---|
| *December No.* Meeting June 28, 1958 | | |
| Meeting at the Royal National Orthopædic Hospital, Stanmore | | |
| OSTEOTOMY IN THE TREATMENT OF CONGENITAL DISLOCATION OF THE HIP [*Abridged*]. By David Trevor, M.S., F.R.C.S. .. .. .. | 27 | 1045 |

## Section of Otology

| | | |
|---|---|---|
| *January No.* Meeting Nov. 1, 1957 | | |
| OTOSCLEROSIS, A TWENTY-YEAR RETROSPECT. President's Address by I. Simson Hall, F.R.C.P.Ed., F.R.C.S.Ed... .. .. .. | 1 | 57 |
| *January No.* Meeting Dec. 6, 1957 | | |
| Discussion (*By Title*) .. .. .. | 5 | 61 |
| *August No.* Meeting Feb. 7, 1958 | | |
| Discussion (*By Title*) .. .. .. | 7 | 617 |
| *August No.* Meeting March 7, 1958 | | |
| List of Short Papers Read .. .. | 7 | 617 |
| *August No.* Meeting May 2, 1958 | | |
| DISCUSSION ON THE CONSERVATIVE MANAGEMENT OF MÉNIÈRE'S DISEASE .. .. .. .. | 7 | 617 |
| Dr. R. B. Lumsden .. .. | 7 | 617 |
| Mr. M. Spencer Harrison and Dr. L. Naftalin .. .. .. | 14 | 624 |
| Dr. G. D. McDowall .. .. | 25 | 635 |
| Mr. Thomas J. Wilmot, Mr. Charles Smith .. .. .. | 28 | 638 |

### Section of Otology with Section of Laryngology

| | | |
|---|---|---|
| Joint Summer Meeting held at the Royal College of Surgeons of Edinburgh | | |
| OTOLOGICAL SESSION | | |
| *November No.* Meeting June 27, 1958 | | |
| DISCUSSION ON ACOUSTIC NEUROMA | 29 | 889 |
| Dr. M. R. Dix and Dr. C. S. Hallpike .. .. .. .. | 29 | 889 |
| Professor Norman M. Dott .. | 37 | 897 |
| Mr. William McKenzie .. .. | 38 | 898 |
| Dr. Dix, Mr. T. A. Clarke, Mr. I. B. Thorburn, Professor Dott, Dr. J. D. Hood .. .. .. | 39 | 899 |
| FACIAL PARALYSIS—RESTITUTION BY EXTRA-PETROUS NERVE GRAFT. By Professor Norman M. Dott, C.B.E., F.R.C.S.Ed... .. .. .. | 40 | 900 |
| LARYNGOLOGICAL SESSION | | |
| *November No.* Meeting June 28, 1958 | | |
| Discussion and Paper (*By Title*) .. | 42 | 902 |

## Section of Pædiatrics

| | | |
|---|---|---|
| *April No.* Meeting Oct. 25, 1957 | | |
| DISCUSSION ON THE MOUTH-BREATHER | 1 | 279 |
| Mr. E. Gwynne-Evans .. .. | 1 | 279 |
| Professor C. F. Ballard .. .. | 4 | 282 |
| *April No.* Meeting Nov. 22, 1957 | | |
| THREE CASES OF CHERUBISM (One previously shown in January 1954). By A. White Franklin, M.B., F.R.C.P. .. .. .. .. | 8 | 286 |
| MALIGNANT HÆMANGIOENDOTHELIOMATA SIMULATING MILIARY TUBERCULOSIS AND NEUROBLASTOMA OF THE ADRENAL. By John Lorber, M.D., M.R.C.P., and A. G. Ackerley, F.R.C.S. .. .. | 10 | 288 |
| NEONATAL THROMBOCYTOPENIC PURPURA WITH HÆMANGIOMATA. By Jean M. Smellie, M.A., B.M., M.R.C.P., D.C.H. (for B. E. Schlesinger, O.B.E., M.D., F.R.C.P.) .. .. .. .. | 12 | 290 |
| THYROTOXICOSIS IN A MONGOL. By J. H. Diggle, M.B., M.R.C.P., and R. S. Weetch, M.B., M.R.C.P. (for T. Colver, M.D.) .. .. .. | 15 | 293 |
| SYMPTOMLESS HYPOPLASIA OF ONE THENAR EMINENCE IN CHILDHOOD—THE PRESENTING FEATURE OF A BIZARRE DEVELOPMENTAL SYNDROME (Two Cases).—Trevor P. Mann, M.D. .. .. .. | 16 | 294 |
| TROPICAL EOSINOPHILIA. By C. W. Kesson, M.D. .. .. .. | 18 | 296 |
| List of other Cases shown .. .. | 18 | 296 |
| *June No.* Meeting Jan. 24, 1958 | | |
| DISCUSSION ON THE PREVENTION OF ACCIDENTS IN CHILDHOOD.. .. | 19 | 395 |
| Dr. C. A. Boucher .. .. | 19 | 395 |
| Mr. D. MacG. Jackson .. .. | 20 | 396 |
| Professor S. D. M. Court, Dr. L. Colebrook, Dr. D. MacCarthy | 26 | 402 |
| *September No.* Meeting Feb. 28, 1958 | | |
| Meeting at the Hospital for Sick Children, Great Ormond Street, London | | |
| ULCERATIVE COLITIS IN CHILDHOOD AND A FOLLOW-UP STUDY [*Summary*]. By B. Schlesinger, O.B.E., M.D., F.R.C.P., and J. Platt, B.A., B.M., B.Ch., M.R.C.P. .. .. | 27 | 733 |
| List of Demonstrations .. .. | 29 | 735 |
| *September No.* Meeting March 28, 1958 | | |
| RECURRENT HYPERTROPHIC POLYNEURITIS. By Philip R. Clay, M.R.C.P. (for Hugh Ellis, M.D.) | 29 | 735 |

| | PAGE Sect. | Vol. |
|---|---|---|
| SYNDROME OF OSTEOPOROSIS, CALCIFICATION OF THE BASAL GANGLIA, DWARFISM, MENTAL RETARDATION AND VENTRICULAR SEPTAL DEFECT. By P. F. Benson, M.R.C.P. (for R. E. Bonham Carter, F.R.C.P.) .. | 30 | 736 |
| MARTIN'S SYNDROME DIAGNOSED BY FINDING HEINZ BODIES IN THE PERIPHERAL BLOOD. By D. G. Cottom, M.R.C.P. (for R. E. Bonham Carter, F.R.C.P.) .. | 32 | 738 |
| JUVENILE DISSEMINATED SCLEROSIS. By R. H. R. White, M.A., M.B., M.R.C.P., D.C.H. (for P. R. Evans, M.D., M.Sc., F.R.C.P.) .. | 33 | 739 |
| VITAMIN-D-RESISTANT RICKETS WITH CRANIOSTENOSIS. By K. Hugh-Jones, M.D., M.R.C.P. (for C. F. Harris, M.D., F.R.C.P.) .. .. | 34 | 740 |
| THORACIC NEUROBLASTOMA, TREATED WITH VITAMIN $B_{12}$. By O. D. Fisher, M.R.C.P. .. .. .. | 36 | 742 |
| HYPERTROPHY OF RIGHT CALF MUSCLES. By O. D. Fisher, M.R.C.P. .. .. .. .. | 36 | 742 |
| L.E. CELL PHENOMENON ASSOCIATED WITH CHRONIC HEPATITIS. By C. Upjohn, M.D. (for J. N. O'Reilly, D.M.) .. .. .. .. | 36 | 742 |
| *November No.* Meeting April 18, 1958 | | |
| BLADDER NECK OBSTRUCTION. By D. Innes Williams, F.R.C.S. .. | 37 | 957 |
| *Bacillus fæcalis alcaligenes* SEPTICÆMIA IN THE NEWBORN. By S. A. Doxiadis, M.D., with the co-operation of M. Pavlatou, M.D., and O. Chryssostomidou, M.D. . | 39 | 959 |
| CUTANEOUS GANGRENE. By K. W. Lovel, M.R.C.P. .. .. .. | 42 | 962 |
| *December No.* Meeting June 28, 1958 | | |
| Meeting Held at Bristol | | |
| THE TREATMENT OF PHENYLKETONURIA. By F. S. W. Brimblecombe, M.D., and Margaret E. R. Stoneman, M.B. .. .. .. .. | 45 | 1019 |
| HYPERBILIRUBINÆMIA IN PREMATURE INFANTS TREATED BY EXCHANGE BLOOD TRANSFUSION. By Beryl D. Corner, M.D., F.R.C.P. .. .. | 45 | 1019 |
| HEART FAILURE IN INFANTS. By K. Simpson, M.D. .. .. .. | 48 | 1022 |
| A COMMON DENOMINATOR IN THE RECURRENT PAINS OF CHILDHOOD. By John Apley, M.D. .. .. | 49 | 1023 |
| THE VASCULAR FACTOR IN BIRTH INJURY. By A. V. Neale, M.D., and H. Urich, M.D. .. .. .. | 50 | 1024 |
| PERITONEAL DRAINAGE IN THE TREATMENT OF HYDROCEPHALUS. By G. L. Alexander, B.Sc., M.D., F.R.C.S., D. G. Phillips, M.B., F.R.C.S., D.L.O., and A. Hulme, M.B., F.R.C.S. .. .. .. | 51 | 1025 |
| SOME OBSERVATIONS ON AVIAN OSTEOPETROSIS. By J. R. Holmes, M.V.Sc., Ph.D., M.R.C.V.S. .. | 52 | 1026 |
| REGIONAL ILEITIS IN CHILDREN. By C. H. Talbot, F.R.C.S. .. .. | 53 | 1027 |


## Section of Pathology


| | PAGE Sect. | Vol. |
|---|---|---|
| *May No.* Meeting Nov. 19, 1957 | | |
| DIABETES INSIPIDUS: THE CONTRIBUTION OF HISTOCHEMICAL AND ISOTOPE TECHNIQUES TO THE INVESTIGATION OF ITS PATHOGENESIS. By J. C. Sloper, M.D. .. .. | 1 | 335 |
| THE APPLICATION OF HISTOCHEMICAL METHODS FOR PROTEIN IDENTIFICATION IN THE STUDY OF CERTAIN PATHOLOGICAL PROBLEMS. By C. W. M. Adams, M.B., B.Ch. .. | 5 | 339 |
| [1]SOME HISTOCHEMICAL ASPECTS OF PÆDIATRIC PATHOLOGY, WITH REMARKS ON QUANTITATION IN HISTOCHEMISTRY. By Irvine J. Hunter, M.B., B.Sc. .. .. .. .. | 9 | 343 |
| *May No.* Meeting Jan. 21, 1958 | | |
| THE PROBLEM OF CANCER OF THE LUNG IN THE INDUSTRIAL AREA OF LIÈGE DURING RECENT YEARS. By Professor J. Firket .. .. .. | 13 | 347 |
| *July No.* Meeting Feb. 4, 1958 | | |
| THE ROLE OF FUNGI AS HUMAN PATHOGENS. By R. W. Riddell, M.D., F.R.C.P.Ed. .. .. | 19 | 491 |
| OBSERVATIONS ON A CASE OF TORULOSIS ASSOCIATED WITH HODGKIN'S DISEASE. By N. F. C. Gowing, M.D. .. .. .. .. | 22 | 494 |
| AN EXPERIMENTAL APPROACH TO THE STUDY OF INFECTIONS BY YEAST-LIKE ORGANISMS. By H. I. Winner, M.D. .. .. .. .. | 24 | 496 |
| MULTIPLE FUNGOUS INFECTIONS OF SKIN. By Betty M. Partridge, M.A. | 27 | 499 |
| THE OCCURRENCE OF *Aspergillus fumigatus* IN RESPIRATORY INFECTIONS. By Yvonne M. Clayton, B.Sc. .. .. .. .. | 29 | 501 |
| *September No.* Meeting March 18, 1958 | | |
| FOLIC ACID DEFICIENCY AND THE MEGALOBLASTIC ANÆMIAS. By I. Chanarin, M.D., D.C.P., D. L. Mollin, M.B., and B. B. Anderson, B.Sc. .. .. .. .. | 31 | 757 |


[1]*See also* p. 1048 (Dec. No.)

| | PAGE Sect. | Vol. |
|---|---|---|
| HYPOPLASTIC ANÆMIA IN INFANCY. By John L. Stafford, M.B. .. | 37 | 763 |
| PRIMARY HÆMORRHAGIC THROMBOCYTHÆMIA. By Sidney Shaw, M.D., and R. A. M. Oliver, M.A., D.M. | 42 | 768 |
| **Section of Comparative Medicine with Section of Pathology** | | |
| (*JOINT MEETING No.* 1) | | |
| *September No.* Meeting April 16, 1958 | | |
| DISCUSSION ON RECENT ADVANCES IN DEMYELINATING DISEASE .. .. | — | 745 |
| EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS AND ITS IMMUNOCHEMISTRY. By Jack Colover, M.D., M.R.C.P. .. .. .. .. | — | 745 |
| RECENT ADVANCES IN SWAYBACK. By R. M. Barlow, B.Sc., M.R.C.V.S. | — | 748 |
| DEMYELINATING DISEASE: THE PRESENT SITUATION. By Professor C. E. Lumsden, M.D. .. .. | — | 752 |
| **Section of Physical Medicine** | | |
| *February No.* Meeting Oct. 9, 1957 | | |
| DISCUSSION ON NERVE PRESSURE SYNDROMES .. .. .. .. | 1 | 87 |
| Dr. I. Meanock .. .. .. | 1 | 87 |
| Dr. R. W. Gilliatt .. .. .. | 5 | 91 |
| *February No.* Meeting Nov. 13, 1957 | | |
| DISCUSSION: HYDROTHERAPY. IS IT OF VALUE? .. .. .. .. | 8 | 94 |
| Dr. R. Harris .. .. .. | 8 | 94 |
| Dr. J. H. Jacobs .. .. .. | 11 | 97 |
| Dr. T. G. Reah .. .. .. | 12 | 98 |
| Dr. Harris .. .. .. .. | 14 | 100 |
| *April No.* Meeting Dec. 11, 1957 | | |
| DISCUSSION ON NON-ARTICULAR RHEUMATISM .. .. .. | 15 | 251 |
| Dr. B. G. B. Christie .. .. | 15 | 251 |
| Dr. Hugh Burt .. .. .. | 19 | 255 |
| *May No.* Meeting Jan. 8, 1958 | | |
| DISCUSSION ON THE COMPLICATIONS OF STEROID THERAPY .. .. | 23 | 313 |
| Dr. J. P. Currie .. .. .. | 23 | 313 |
| Dr. John H. Glyn .. .. .. | 24 | 314 |
| Dr. E. V. B. Morton .. .. | 27 | 317 |
| *September No.* Meeting March 12, 1958 | | |
| Samuel Hyde Memorial Lecture [Number 12] | | |
| ON THE FRINGES OF ELECTRODIAGNOSIS. By P. Bauwens, M.R.C.P. | 31 | 725 |
| **Section of Proctology** | | |
| *April No.* Meeting Nov. 13, 1957 | | |
| POLYPOSIS INTESTINI [*Abridged*]. President's Address by Henry R. Thompson, M.A., M.B., F.R.C.S. | 1 | 241 |
| *April No.* Meeting Jan. 8, 1958 | | |
| ILEO-CÆCAL TUBERCULOSIS. By H. R. Thompson, F.R.C.S., and B. C. Morson, D.M. .. .. .. | 6 | 246 |
| TWO UNUSUAL CASES OF RECTO-SIGMOID CARCINOMA WITH BLADDER INVOLVEMENT. By A. N. Smith, F.R.C.S. (for H. R. Thompson, F.R.C.S.) .. .. .. .. | 6 | 246 |
| DIVERTICULITIS OF COLON. By Bruce Bomford, F.R.C.S. (for Harold Dodd, F.R.C.S.) .. .. .. | 7 | 247 |
| CROHN'S DISEASE AND COLITIS. By C. I. Cooling, F.R.C.S. (for Ronald W. Raven, O.B.E., F.R.C.S.) .. | 7 | 247 |
| CROHN'S DISEASE OF THE RECTUM. By H. W. A. Baron, F.R.C.S. .. | 7 | 247 |
| ANO-RECTAL MELANO-SARCOMA. By Frank Forty, F.R.C.S. .. .. | 8 | 248 |
| LYMPHOSARCOMA OF RECTUM. By H. Gordon Ungley, F.R.C.S. .. | 8 | 248 |
| POLYPOSIS COLI WITH SEVERAL AREAS OF CARCINOMATOUS DEGENERATION. By R. V. Cooke, Ch.M. .. .. | 8 | 248 |
| COMPLETE RECTAL PROLAPSE FOLLOWING OPERATION FOR A TUMOUR OF THE CAUDA EQUINA. By E. C. B. Butler, F.R.C.S. .. .. .. | 9 | 249 |
| PNEUMATOSIS CYSTOIDES INTESTINALIS. By Harold C. Edwards, C.B.E., M.S. .. .. .. .. .. | 9 | 249 |
| IDIOPATHIC GANGRENE OF THE COLON. By B. J. Fowler, F.R.C.S. (for H. Blacow Yates, F.R.C.S.) .. | 10 | 250 |
| LOCALIZED BENIGN ULCERATION OF THE COLON WITH UNUSUAL FEATURES. By J. A. Lloyd Davies, M.B., B.S., F.R.C.S. .. .. | 10 | 250 |
| *June No.* Meeting Feb. 12, 1958 | | |
| ANO-RECTAL ANATOMY. By Professor E. W. Walls, M.D.. .. .. .. | 11 | 425 |
| THE PEUTZ-JEGHERS SYNDROME. By Thomas L. Dormandy, M.B., B.Sc., F.R.C.S.Ed.. .. .. .. | 12 | 426 |
| TREATMENT OF ULCERATIVE COLITIS WITH LOCAL HYDROCORTISONE. By S. C. Truelove, M.D., M.R.C.P. .. | 15 | 429 |
| OBSERVATIONS ON THE MANAGEMENT OF IDIOPATHIC PROCTITIS [*Abridged*]. By A. C. Newell, M.D., M.R.A.C.P., and F. Avery Jones, M.D., F.R.C.P. | 17 | 431 |
| *October No.* Meeting May 14, 1958 | | |
| DISCUSSION ON COMPLICATIONS OF EXCISION OF THE RECTUM .. .. | 19 | 865 |
| Dr. Ronald Jarman, Dr. W. Kirk Rae .. .. .. .. | 19 | 865 |

| | PAGE Sect. | Vol. |
|---|---|---|
| Mr. Gordon S. Ramsay .. .. | 21 | 867 |
| Mr. J. M. Davis .. .. .. | 24 | 870 |
| Mr. D. Innes Williams .. .. | 26 | 872 |
| Mr. C. I. Cooling .. .. .. | 28 | 874 |
| Mr. H. Gordon Ungley, Professor J. C. Goligher, Mr. C. Patrick Sames .. .. .. .. | 31 | 877 |


## Section of Psychiatry


*February No.* Meeting Oct. 8, 1957

| | | |
|---|---|---|
| REFLECTIONS ON THE UNDERGRADUATE AND POSTGRADUATE TEACHING OF PSYCHIATRY [*Abstract*]. President's Address by Professor E. Stengel, M.D., M.R.C.P. .. .. .. | 1 | 75 |

*February No.* Meeting Nov. 12, 1957

| | | |
|---|---|---|
| DISCUSSION ON PHYSIOLOGICAL MEASUREMENTS OF "EMOTIONAL TENSION" .. .. .. .. | 2 | 76 |
| Dr. Brian Ackner .. .. .. | 2 | 76 |
| Dr. G. Pampiglione .. .. | 5 | 79 |
| Dr. Peter Sainsbury .. .. | 7 | 81 |
| Dr. Denis Hill .. .. .. | 11 | 85 |
| Dr. Murdo Mackenzie .. .. | 12 | 86 |

*April No.* Meeting Jan. 14, 1958

| | | |
|---|---|---|
| DISCUSSION ON THE LEGAL ASPECTS OF SUICIDAL ACTS .. .. .. | 13 | 297 |
| Dr. Doris Odlum .. .. .. | 13 | 297 |
| Dr. P. Epps .. .. .. .. | 14 | 298 |
| Dr. I. R. C. Batchelor .. .. | 17 | 301 |
| Dr. Irene M. H. MacAdam, J.P... | 18 | 302 |

*November No.* Meeting April 8, 1958

| | | |
|---|---|---|
| THE POST-OPERATIVE PSYCHOSES [*Summary*]. By B. B. Zeitlyn, M.D., D.P.M. .. .. .. .. | 21 | 937 |

*November No.* Meeting May 13, 1958

| | | |
|---|---|---|
| CLINICAL STUDIES IN PSYCHO-ANALYSIS (RESEARCH PROJECT OF THE HAMPSTEAD CHILD-THERAPY CLINIC). By Anna Freud, LL.D. .. .. | 22 | 938 |
| Dr. Ilse Hellman .. .. .. | 26 | 942 |
| Mrs. Dorothy Burlingham .. | 27 | 943 |
| Dr. L. Frankl .. .. .. | 29 | 945 |
| Dr. C. de Monchaux .. .. | 30 | 946 |

*November No.* Meeting June 10, 1958

Meeting at the Royal Infirmary, Sheffield

| | | |
|---|---|---|
| DISCUSSION ON METHODS OF PSYCHOSOMATIC MEDICINE .. .. .. | 31 | 947 |
| Dr. Denis Leigh .. .. .. | 31 | 947 |
| Dr. Joseph Sandler .. .. | 32 | 948 |
| Dr. Max Hamilton, Dr. R. H. Gosling .. .. .. .. | 33 | 949 |


## Section of Radiology


| | PAGE Sect. | Vol. |
|---|---|---|

*February No.* Meeting Oct. 18, 1957

| | | |
|---|---|---|
| THE PRESENT ROLE OF SURGERY IN CARCINOMA OF THE BREAST [*Précis*]. By E. Stanley Lee, M.S., F.R.C.S. | 1 | 119 |
| THE COMPARISON OF TWO RADIOTHERAPY TECHNIQUES IN BREAST CARCINOMA [*Abridged*]. By R. W. Gunderson, F.R.C.S., F.F.R. .. | 2 | 120 |
| THE VALUE OF HISTOLOGY IN THE PROGNOSIS AND CLASSIFICATION OF BREAST CANCER. By H. J. G. Bloom, M.D., M.R.C.P., F.F.R... | 4 | 122 |

*February No.* Meeting Nov. 15, 1957

| | | |
|---|---|---|
| VISION, PHOTOGRAPHY AND ELECTRONICS IN RADIOLOGY [*Précis*]. By G. E. Donovan, M.D., M.Sc., D.P.H., and E. Stafford, B.Sc., B.A. .. .. .. .. .. | 8 | 126 |

*July No.* Meeting Jan. 17, 1958

| | | |
|---|---|---|
| SURGICAL CONSIDERATIONS IN TREATMENT OF MALIGNANT DISEASE OF THE THYROID GLAND. By Geraldine Barry, M.S., F.R.C.S. .. .. | 9 | 521 |
| RADIOTHERAPY FOR MALIGNANT TUMOURS OF THE THYROID. By G. W. Blomfield, M.A., F.R.C.S., M.R.C.O.G., F.F.R. .. .. | 10 | 522 |
| RADIOIODINE IN THE TREATMENT OF THYROID CARCINOMA. By A. W. G. Goolden, M.B., B.S., D.M.R.T... | 13 | 525 |

*October No.* Meeting Feb. 21, 1958

| | | |
|---|---|---|
| BENIGN LESIONS OF THE PYLORIC ANTRUM SIMULATING CARCINOMA [*Summary*]. By J. N. Pattinson, M.B., F.F.R., and G. Osborne, M.D., M.R.C.P., D.M.R.D. .. | 17 | 789 |
| THE RADIOLOGICAL DIAGNOSIS OF MALIGNANT GASTRIC ULCER [*Summary*]. By B. Green, M.R.C.S., L.R.C.P., D.M.R.D., and R. A. Kemp Harper, M.D. .. .. | 17 | 789 |
| HEADACHE AND GASTRIC EMPTYING TIME. By L. S. Carstairs, M.B., B.S., D.M.R. .. .. .. | 18 | 790 |

*October No.* Meeting April 18, 1958

| | | |
|---|---|---|
| SOME RADIOLOGICAL ASPECTS OF BILIARY TRACT DISEASE [*Abridged*]. President's Address by E. Duff Gray, M.A., M.D. .. .. | 21 | 793 |

*November No.* Meeting March 21, 1958

| | | |
|---|---|---|
| DISCUSSION ON PITUITARY TUMOURS | 25 | 907 |
| Mr. Harvey Jackson .. .. | 25 | 907 |
| Mr. J. Jackson Richmond .. | 29 | 911 |
| Dr. S. Leonard Simpson .. .. | 33 | 915 |

## Section of Surgery


| | PAGE Sect. | Vol. |
|---|---|---|
| *January No.* Meeting Oct. 2, 1957 | | |
| DISCUSSION ON HIATUS HERNIA .. | 1 | 31 |
| Mr. Norman C. Tanner .. .. | 1 | 31 |
| Mr. R. H. Franklin .. .. | 4 | 34 |
| Mr. Vernon C. Thompson .. | 5 | 35 |
| Mr. Donald Barlow .. .. | 7 | 37 |
| *January No.* Meeting Nov. 6, 1957 | | |
| List of Specimens shown .. .. | 8 | 38 |
| *June No.* Meeting Dec. 4, 1957 | | |
| TRANSATLANTIC DISCUSSION ON ADVANCES IN CHEMOTHERAPY OF CANCER .. .. .. .. | 9 | 409 |
| Dr. Leandro M. Tocantins, Mr. A. Dickson Wright .. .. | 9 | 409 |
| Dr. Sidney Farber, Dr. Eve Wiltshaw .. .. .. .. | 10 | 410 |
| Dr. Emil Frei .. .. .. | 11 | 411 |
| Professor Alexander Haddow .. | 12 | 412 |
| Dr. Philip Custer .. .. .. | 13 | 413 |
| Dr. R. Bodley Scott, Dr. Howard Skipper .. .. .. .. | 14 | 414 |
| Professor Haddow, Dr. Joseph Burchenal .. .. .. | 16 | 416 |
| Dr. John F. Wilkinson .. .. | 17 | 417 |
| Dr. Bodley Scott, Dr. Wiltshaw, Dr. Frei .. .. .. .. | 18 | 418 |
| Dr. Farber, Professor Haddow, Dr. Custer, Dr. Bodley Scott, Dr. Frei .. .. .. .. | 19 | 419 |
| Dr. Burchenal, Dr. Skipper, Professor Haddow .. .. .. | 20 | 420 |
| *July No.* Meeting Jan. 8, 1958 | | |
| Meeting held at St. Mary's Hospital, London | | |
| List of Operations, Demonstrations and Short Papers .. .. .. | 21 | 503 |
| *July No.* Meeting Feb. 5, 1958 | | |
| DISCUSSION ON SMALL BOWEL OBSTRUCTION [*Abridged*] .. .. | 21 | 503 |
| Mr. Robert V. Cooke .. .. | 21 | 503 |
| Mr. P. T. Savage .. .. .. | 25 | 507 |
| *September No.* Meeting March 5, 1958 | | |
| DISCUSSION ON HAND INJURIES .. | 27 | 713 |
| Dr. M. Iselin .. .. .. | 27 | 713 |
| Mr. John N. Barron .. .. | 29 | 715 |
| Mr. L. W. Plewes .. .. .. | 30 | 716 |
| *October No.* Meeting April 2, 1958 | | |
| THE POST-AURICULAR WOLFE GRAFT AND ITS USE IN THE TREATMENT OF MALIGNANT ULCERATION OF THE FACE. By J. C. M. Currie, M.B., B.Chir. (for Alan Hunt, M.Ch.).. | 33 | 815 |
| PERSISTENT VARICOSE VEINS WITH SPECIAL REFERENCE TO THE VARICOSE TRIBUTARIES OF THE SUPERFICIAL FEMORAL AND POPLITEAL VEINS. By Harold Dodd, Ch.M., F.R.C.S. .. .. .. .. | 35 | 817 |
| Film (*By title*) .. .. .. .. | 38 | 820 |


## United Services Section


| | PAGE Sect. | Vol. |
|---|---|---|
| *January No.* Meeting Oct. 3, 1957 | | |
| THE PROBLEM OF NOISE IN THE ROYAL AIR FORCE. By Wing Commander P. F. King, F.R.C.S.Ed., D.L.O., and Flight Lieutenant R. P. Gannon, B.Sc., M.B., Ch.B. .. | 1 | 45 |
| *February No.* Meeting Dec. 5, 1957 | | |
| SUBMARINE MEDICINE ON U.S.S. NAUTILUS AND U.S.S. SEAWOLF. By Lt. Cdr. John H. Ebersole .. | 9 | 63 |
| *June No.* Meeting March 6, 1958 | | |
| DISCUSSION ON INFLUENZA .. .. | 21 | 447 |
| Major R. J. C. Hart, R.A.M.C. .. | 21 | 447 |
| Surgeon-Major G. H. Bulow .. | 24 | 450 |
| Lt.-Col. R. M. Johnstone, M.B.E., M.C., R.A.M.C.. .. .. | 25 | 451 |
| Colonel T. A. Pace, O.B.E., M.D., B.Sc., D.P.H. .. .. .. | 26 | 452 |
| *October No.* Meeting June 5, 1958 | | |
| DISCUSSION: UNDERWATER EMERGENCIES IN THE ROYAL NAVY .. .. | 29 | 821 |
| Surg. Cdr. S. Miles, R.N.. .. | 29 | 821 |
| Surg. Lt. R. J. W. Lambert, R.N. | 32 | 824 |
| Surg. Lt. Cdr. J. S. P. Rawlins, R.N., M.B.E. .. .. .. | 36 | 828 |
| *December No.* Meeting Oct. 2, 1958 | | |
| A REVIEW OF HÆMODIALYSIS IN RENAL FAILURE AND SOME POINTS IN THE DIAGNOSIS OF ACUTE RENAL FAILURE. By A. M. Joekes, M.R.C.P. .. .. .. .. | 39 | 1069 |
| Paper (*By Title*) .. .. .. | 40 | 1070 |
| EXPERIENCES WITH THE KOLFF TWIN COIL ARTIFICIAL KIDNEY AT THE RENAL UNIT, PRINCESS MARY'S ROYAL AIR FORCE HOSPITAL, HALTON. By Group Captain R. C. Jackson, M.R.C.P.Ed. .. .. | 41 | 1071 |


## Section of Urology


| | PAGE Sect. | Vol. |
|---|---|---|
| *March No.* Meeting Oct. 24, 1957 | | |
| THE CALCIUM-CONTAINING RENAL STONE [*Abridged*]. President's Address by Leslie N. Pyrah, M.Sc., Ch.M., F.R.C.S. .. .. .. | 1 | 183 |
| *March No.* Meeting Nov. 28, 1957 | | |
| List of Specimens shown .. .. | 18 | 200 |
| *May No.* Meeting Jan. 23, 1958 | | |
| URINARY COLLOIDS [*Abstract*]. By N. F. Maclagan, M.D., D.Sc., F.R.C.P. .. .. .. .. | 19 | 327 |
| BILATERAL ORCHIDOPEXY AND FERTILITY. By J. H. Carver, T.D., F.R.C.S. .. .. .. .. | 20 | 328 |

| | PAGE Sect. | Vol. |
|---|---|---|
| BACTERIÆMIA AND SEPTICÆMIA AFTER UROLOGICAL OPERATIONS. By N. Slade, M.B., F.R.C.S. .. .. | 23 | 331 |
| *May No.* Meeting Feb. 27, 1958 | | |
| List of Specimens shown .. .. | 26 | 334 |
| *September No.* Meeting March 27, 1958 | | |
| SYMPOSIUM ON LOWER THIRD OF URETER .. .. .. .. | 27 | 773 |
| Professor G. Causey .. .. | 27 | 773 |
| Mr. G. F. Murnaghan .. .. | 30 | 776 |
| Mr. Howard G. Hanley .. .. | 34 | 780 |
| Mr. F. P. Raper .. .. .. | 35 | 781 |
| Mr. D. Innes Williams .. .. | 37 | 783 |
| *November No.* Meeting April 25, 1958 | | |
| Meeting at the General Infirmary, Leeds | | |
| THE CAUSES OF DEATH IN 14 CASES OF ACUTE RENAL FAILURE [*Summary*]. By C. K. Anderson, M.B.. . .. | 39 | 965 |
| THE GENESIS OF TUMOURS OF THE BLADDER AND OTHER TISSUES WITH SPECIAL REFERENCE TO THE INDUSTRIAL AMINES. By G. M. Bonser, M.D., F.R.C.P., M.R.C.S., D. B. Clayson, B.A., Ph.D., J. W. Jull, B.Sc., Ph.D., and L. N. Pyrah, M.Sc., Ch.M., F.R.C.S. .. .. | 39 | 965 |
| THE URINARY EXCRETION OF OXALIC ACID IN NEPHROLITHIASIS. By A. Hodgkinson, B.Sc., Ph.D., A.R.I.C. | 44 | 970 |
| *December No.* Meeting April 25, 1958, *contd.* | | |
| Meeting at the General Infirmary, Leeds | | |
| ELECTIVE PROSTATECTOMY. By Professor E. Wildbolz .. .. .. | 47 | 1029 |
| *December No.* Meeting May 22, 1958 | | |
| VESICO-INTESTINAL FISTULA [*Abridged*] | 50 | 1032 |
| Mr. H. E. Lockhart-Mummery .. | 50 | 1032 |
| Mr. J. D. Fergusson .. .. | 55 | 1037 |
| Mr. C. G. Scorer .. .. .. | 60 | 1042 |


## Joint Meetings


**Section of Comparative Medicine with Section of Pathology**

(*JOINT MEETING No.* 1)

| | PAGE Sect. | Vol. |
|---|---|---|
| *September No.* Meeting April 16, 1958 | | |
| DISCUSSION ON RECENT ADVANCES IN DEMYELINATING DISEASE .. .. | — | 745 |
| EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS AND ITS IMMUNOCHEMISTRY. By Jack Colover, M.D., M.R.C.P. | — | 745 |
| RECENT ADVANCES IN SWAYBACK. By R. M. Barlow, B.Sc., M.R.C.V.S. | — | 748 |
| DEMYELINATING DISEASE: THE PRESENT SITUATION. By Professor C. E. Lumsden, M.D. .. .. .. | — | 752 |

**Section of Experimental Medicine and Therapeutics with Section of Neurology**

(*JOINT MEETING No.* 2)

| | | |
|---|---|---|
| *December No.* Meeting May 13, 1958 | | |
| DISCUSSION ON TETANUS .. .. | — | 997 |
| Professor G. Payling Wright .. .. | — | 997 |
| Dr. D. R. Laurence .. .. | — | 1000 |
| Professor E. B. Adams .. .. | — | 1002 |
| Dr. A. Crampton Smith .. .. | — | 1006 |


Printed in England by Staples Printers Limited, at their Great Titchfield Street, London, establishment.

# Section of Comparative Medicine

President—J. B. Brooksby, D.Sc., Ph.D., M.R.C.V.S.

[*October* 16, 1957]

## Comparative Aspects in Virology

### PRESIDENT'S ADDRESS

By J. B. Brooksby, D.Sc., Ph.D., M.R.C.V.S.

#### Introduction

An interesting feature of virology is that the overlap of interest between the medical and veterinary fields is perhaps greater than in many other basic studies of human and veterinary medicine. Several diseases occur in both man and animals, but this does not explain why illustrations in medical texts on virology are frequently drawn from veterinary medicine and vice versa.

Two major aspects only will be discussed—modified strains and their use in immunization, and basic studies on structure, especially with regard to biological properties.

#### Modified Strains and Their Use in Immunization

The use of modified strains for immunizing purposes is one of the oldest concepts in virology. Since the number of instances of use of such strains is increasing, particularly in the veterinary field, some consideration of the nature and properties of modified strains seems to be necessary.

The selection of naturally occurring strains of low virulence, such as vaccinia, is historically ancient. All virologists are acquainted with variation in virulence as between different field strains of viruses. In some cases this may be manifested in a virus which attacks more than one host species, as normal virulence for one species and almost complete non-infectivity for another. An example of this phenomenon is the cattle adaptation and swine adaptation of some strains of foot-and-mouth disease. This has its epidemiological significance in outbreaks of disease confined to cattle and to swine respectively. Such strains can be regarded as naturally modified strains. There is here a natural method of genetic selection of the strain, due to the factors of difference in the hosts. No such method would seem to exist with viruses with a single host, and it is therefore left to the virologist to arrange the conditions so that if modifications arise, the environment will favour their survival. In time, the strain will become relatively homogeneous in respect of the characters desired. In this paper the various processes of modification are considered more from the practical point of view than from the fundamental principles involved.

The simplest technique for production of modified strains, which hardly seems to imply

actual interference by the virologist, is the selection of strains of low virulence which either exist in the wild strain or are very readily produced from it. Examples of these are the Newcastle disease vaccine strains used in mass immunizing procedures in the U.S.A. and the modified poliomyelitis strains of Sabin (1955) and Koprowski (1955). Sabin passaged virus in tissue culture and segregated variants, first by a dilution technique, and finally by isolation of individual plaques. The tests of such strains have been discussed at length at Geneva, and perhaps the most important criterion required of them, apart from lowered initial virulence, is that strains isolated from vaccinated individuals must still show some attenuation. The general feeling is against wide use of such modified strains until greater safeguards can be devised.

The second category of modified strains are those which have been artificially produced by adaptation of virus to abnormal hosts, or to tissues not commonly attacked. There is a substantial literature on the strains which have been produced in this way, but the mechanism of the process involved is by no means clear, and indeed there is little information on which techniques may be most effectively used. Some of the factors which may be important in the process of modification of a strain will now be considered.

(1) *The preservation of the antigenic identity of the virus during modification.*—There have been relatively few suggestions that the antigenic identity of a virus has been altered during modification. Hirst (1947) in dealing with mouse-adapted strains of influenza virus demonstrated that two lines derived in mice were antigenically dissimilar, and that each was different from the parent strain from which they were derived. On the other hand the "O" and "D" strains of Burnet and Bull (1943), although different in a hæmagglutinating capacity were antigenically similar. Edwards (1949) suggested that different goat-adapted strains of rinderpest virus had antigenically dissimilar constitution, but the dissimilarity noted might have been due to other factors. Brotherston (1955) with the same virus, compared the antigens of cattle, goat and rabbit strains and believed them to be identical.

In the process of modification it would seem that while many of the characters are labile, the antigenic constitution is remarkably stable. Does this suggest that the antigenic constitution depends on what might be termed the core of the virus, rather than on the outer covering—in terms of Crick and Watson's (1956 and 1957) hypothesis on the ribonucleic acid (R.N.A.) rather than the protein envelope?

(2) *Alteration in tissue tropism of the virus.*—It has sometimes been stated that modified strains might be expected to give their best results if they produced an inapparent infection in a tissue which the virus usually infects. Intranasal strains in influenza, and intestinal strains in poliomyelitis follow this dictum. On the other hand adaptation to another host frequently involves also a change in the tissue tropism of the virus, for example in the neurotropic strains of African horse sickness and of yellow fever. If, then, infection of the usual host takes place it may not involve the tissue normally associated with the infection, but rather produce a new form of the disease in another tissue. Schneider (1956) has described muscular lesions in cattle after inoculation of a myotropic strain of the virus of foot-and-mouth disease modified by passage in mice. If this trend to altered tropism were carried too far, multiplication of the virus at unusual sites might have unfortunate effects in vaccinated animals.

(3) *Significance of age of host in reaction to modified virus.*—Viruses may produce different effects in hosts of different ages. In human medicine the classic example is the effect of rubella on the fœtus. In veterinary medicine the virus of foot-and-mouth disease in the young animal may produce acute lesions in both cardiac and skeletal muscle leading to death. With modified strains there has already been indication of untoward effects. In vaccination of swine with lapinized swine fever vaccine, fœtal defects and increased number of stillbirths were observed, when swine were vaccinated in early pregnancy (Young, 1952). These defects were somewhat milder than might have been expected with an unmodified virus. From the laboratory point of view it is therefore obvious that adequate tests of modified strains in animals of all ages are necessary.

(4) *Fixity of modified strains.*—The fixity of the strain is of primary importance. For some viruses the margin between loss of infectivity on the one hand and loss of immunizing power on the other is a small one, and it is necessary to make sure that the strain will retain its properties once it has been altered. It is difficult to be sure whether some of the field

reports of reversion to full virulence are actually due to alteration in character of the strain or to increased susceptibility of the particular group of animals inoculated. Latent infections may also be brought to light by inoculation of a modified strain and complicate the situation. Occasionally the lapinized swine-fever vaccine gives severe reaction in an inoculated herd. There is no record of examination of the virus in the laboratory following such an event, and it is therefore impossible to determine whether the difficulty has arisen with the virus or with the host. In poliomyelitis, Dick and his colleagues (Dane *et al.*, 1957) have shown quite clearly an increase in virulence for monkeys of the strain after passage through the intestine of children. In the case of rinderpest virus there is clear indication that strains which are quite certainly fixed in character, for example the Nakamura III strain, may produce quite a high mortality in hypersensitive cattle. This has been described for Japanese Black cattle and also for some Korean breeds (Nakamura and Kuroda, 1942). The fixity of this strain was controlled by serial passage in cattle when ten passages had no effect on increasing virulence for cattle (Nakamura *et al.*, 1943). Brotherston (1951) claimed to be able to increase virulence slightly by alternate rabbit and cattle passages.

(5) *Reproducibility of strain modification.*—Reproducibility of the course of modification is of more fundamental interest. In the strains of virus which have been used for immunization in the field, it has frequently been the custom to accept the strain in the phase to which it has been developed, and not to enquire too closely into the stages in its attenuation. The modification of a strain does not seem to mean change in only one character, but rather a summation of changes in several associated characters. It is therefore hardly surprising that the alteration from fully virulent strain to the characteristic modified strain should be a slow process.

One of the most interesting examples where the attenuation of a strain for several different species has been described is the work on the Flury strain of rabies. In its first form this strain was suitable for use in dogs, and of course has had a wide use in that species. Vaccination of cattle with this strain was found to produce clinical signs of rabies. Further serial passage produced strains of lower virulence for various laboratory animals (guinea-pigs and hamsters), and finally a stage was reached at which cattle could be inoculated with safety. In man inoculation of the more attenuated strain followed by the less attenuated strain will give a good immunity.

(6) *Simultaneous modification for more than one host.*—Wide host range is essentially a problem which is of veterinary interest in respect of modified strains. The problem of naturally species-adapted strains in foot-and-mouth disease has already been mentioned. The corollary is the adapted strain which has a lowered pathogenicity for cattle but not for swine. A case in which a modified strain had this property was recently observed by Sellers (unpublished) in our laboratory. This particular strain had been passaged in mice and the virulence greatly reduced for cattle. It was, however, still fully virulent for swine. The second observation, on another strain of another type, had fortuitous success in that the strain had been rendered non-infective for swine and only almost so for cattle. This strain had been passaged in a variety of experimental hosts including both mice and eggs.

## Factors Influencing the Control of Modification of Strains

The problem of estimation of the degree of attenuation which has been achieved is dealt with much more readily in veterinary than in human medicine. It is possible in the last analysis to test the strain in the animal which is the natural host, and it is therefore not necessary to base the probable effect on experimental results in nearly related species. This does not mean that a correlation should not be sought between the results in the natural host and the results in other species which could be used as indicators in the degree of attenuation of the strain. The usefulness of such indicators during the serial passages leading to attenuation is obvious. The detailed history of the attenuation of a strain gives confidence in its probable behaviour.

It is important to consider the role of the host, as the attenuated strain is conceived as invading and multiplying in the vaccinated host. This invasion and multiplication, like any other infection, will be governed by the host susceptibility and invasive power of the virus. Host susceptibility can be observed to vary quite widely in the reactions of individuals to viruses which have not been attenuated. The variation in susceptibility of the host might be expected to become more obvious with attenuated strains of poor invasiveness. Thus it might well be that strains differing quite widely in attenuation produce little difference in

the number of animals infected in given groups of known susceptible animals, if it is once accepted that a small percentage, say 5% are hypersensitive. It must be noted that with non-attenuated strains it is the animals of low susceptibility, resistant animals, which are most readily observed. With the attenuated strains at the time of vaccination the animals of high susceptibility are more obvious. When the time comes for the animals to be challenged it is of course obvious again which animals have been of low susceptibility and fail to become infected by the attenuated strain. Observations on a modified strain of the virus of foot-and-mouth disease illustrate these points. Through a number of serial passages this strain appeared constantly to infect about one out of eight cattle inoculated intradermally in the tongue. In an experiment using a virus dose 1/100 that which infected one of eight animals, two of eight became infected. It seems that host susceptibility rather than degree of attenuation is the operative factor. At the same time this strain failed to immunize about one out of eight animals inoculated, perhaps due to a natural resistance in such cattle.

A possible solution to the problem of infectivity of attenuated strains lies in the administration of the virus by a route other than into the most susceptible tissue. This solution has been tried with a number of viruses, notably with that of infectious laryngo-tracheitis and those neurotropic viruses for which a modified strain is available, such as rabies, and Teschen disease. Modification of the route, however, may not always give the desired result, and cannot be relied upon to make an attenuated strain safer than it otherwise would be in the unattenuated form. A number of workers have drawn attention to the fact that the various respiratory viruses given intramuscularly produce respiratory infection, and some attenuation must be achieved before giving the virus by such a route. On the other hand some strains of the virus of foot-and-mouth disease have been demonstrated to require more than 100,000 times as much virus in order to set up infection by the subcutaneous route as by the intradermal tongue route (Henderson, 1952). These strains were not attenuated and it was found that some animals which failed to react following subcutaneous inoculation did not develop an immunity. The use of an attenuated strain by a route other than the usual one, may fail as an immunizing procedure unless there is some characteristic of the strain which allows it to multiply either at site of inoculation or elsewhere in the body. Very little is known of the tissue propensities of the attenuated strains of most viruses. Research workers have been mainly interested in the fact that they failed to produce the typical disease in the tissue most commonly affected. Nevertheless it would seem to be of great importance to determine where and to what extent attenuated strains multiply in the tissue of the vaccinated host. In work at present in progress in foot-and-mouth disease virus, this stage is about to be reached. Following the work of Skinner (1951) cattle strains of virus have been adapted to the baby mouse and then subsequently to adult mice, which are inoculated intramuscularly. The disease in the mouse is characterized by degeneration of skeletal and cardiac muscle. Skinner (unpublished) has made some interesting experiments on guinea-pigs using such strains. The dermotropic character of the virus in guinea-pigs disappears gradually and progressively on mouse passage. When this modified virus is inoculated intramuscularly, muscular lesions may be produced in young (2–3 weeks) guinea-pigs. In older guinea-pigs, however, no clinical signs are observed, but in both age groups an immunity to intradermal challenge is developed. The dose of virus required to produce this immunity is small, less than 100 I.D.50 for the mouse. Such strains have not yet been fully tested in cattle, although, as in guinea-pigs, their dermotropic characters have been reduced to the point when less than 15% of cattle develop lesions following intradermal inoculation into the tongue. Some strains passaged in eggs also lose their ability to produce clinical infection in cattle.

There may be need for caution in the use of myotropic strains; as mentioned earlier, Schneider obtained lesions in heart and tongue muscles after inoculation of a strain passaged 296 times in mice. Only further experimental work will indicate the probable role of such strains.

Other modified strains in foot-and-mouth disease have been the mouse neurotropic strains of Nagel (1937), and of course the guinea-pig strains which are passaged by the epithelial route. Immunization of cattle by such strains has not been successful.

In at least five cases in veterinary medicine virus passaged in the chick embryo have given attenuated strains which have been used in the field. In foot-and-mouth disease many attempts were made to adapt the virus to the egg before the successful results of Traub and Schneider (1948). Such egg-passaged viruses in foot-and-mouth disease have not generally been regarded as giving a good immunity in cattle, though some results which were limited to groups of two cattle, indicate possible immunizing value. The results quoted earlier of exposure of animals to attenuated strains were, however, produced with a modified strain which, for a great part of its history, had been passaged in eggs.

Skinner (1954) and Gillespie (1954) independently made observations of passage of foot-

and-mouth disease in the young chick. No work has been done on the infectivity of these strains for cattle until recently, when a report appeared on the non-infectivity of a chick strain after 25 serial passages.

I have spoken of the advantages of testing attenuated strains in the susceptible host, but other methods in addition would be useful in screening tests. Pay and Sellers have recently attempted to correlate the cytopathic changes with the pathogenicity of the strain in the natural host species. The results of this in poliomyelitis have been equivocal. In foot-and-mouth disease a range of cells has been used from different hosts—bovine epithelium, bovine kidney, calf kidney, pig kidney—and the cytopathic changes have been correlated with the pathogenicity of the strain in cattle. Strains not pathogenic for cattle have a low cytopathogenicity in bovine and calf kidney, but not necessarily so in pig kidney. Extension of these correlations will be most valuable in observing the alteration of strains during extensive serial passages, which have so far been necessary for attenuation.

The list of veterinary viruses for which attenuated strains are obtainable is already long and appears to be growing. Rinderpest, bluetongue, swine fever, African horse sickness, rabies, distemper, Newcastle disease, fowlpox and infectious bovine rhinotracheitis have all been published, and several more are I believe in course of preparation for publication. The usefulness of most of these vaccines have been assessed in the field, and it is difficult to generalize on the results in a way that one would wish.

With some of the modified strains, notably rinderpest, there has been an acceptance of a calculated risk of producing clinical signs of the disease in a proportion of the animals inoculated. For estimation of efficacy of vaccines, antibody studies of the inoculated animals before and after administration of the strain are indicated, and some very precise idea of the challenge to which the animals are exposed. This would help in comparing the attenuated strains among themselves and also in relation to inactivated vaccines. The laboratory control of these vaccines is by no means easy, and once a strain has been shown to be reasonably safe, it has usually been the practice to accept it without too many further questions as to its origin and whether it could be further modified to increase its efficacy.

## Structure of Virus in Relation to Biological Properties

There is a long list of viruses which show complexity of structure, in that a number of specific particles can be separated from viral suspensions. These particles range from those which are considered as the fully infective particle to smaller ones, whose properties are mainly serological, ranging from hæmagglutination down to complement fixation. The term soluble antigen, which was originally applied by Craigie in vaccinia, has been carried through to the smaller viruses in which the solubility of the small particle is hardly a criterion of differentiation from the large particle. According to the view of the worker, both the smaller and larger could be regarded as either soluble or insoluble. There is a tendency now to refer to the particles in terms of their properties rather than by an arbitrary definition of solubility. The list of viruses in which such complexity exists is a long one, outstanding examples being:

Vaccinia. Mumps. Herpes. Influenza. Yellow fever. Various insect-transmitted encephalitides. Dengue. Poliomyelitis. Foot-and-mouth disease. Newcastle disease virus. Vesicular stomatitis.

Bradish, Brooksby, Dillon and Norambuena (1952) described studies of the sedimentation properties of the virus of foot-and-mouth disease. This work has been extended (Brooksby, 1953, and Bradish, unpublished) and the following summarizes the present position.

In a suspension of the virus of foot-and-mouth disease there are two main particles, separable in the ultracentrifuge:

(1) 70 S component contributing 50% of the complement-fixing activity and most of the infectivity, and

(2) 8 S contributing the other 50% of the complement-fixing activity and less than 1/10,000 of the infectivity.

Another particle of intermediate and indeterminate size is the subject of current research.

In fresh unfractionated virus preparation, the two major components exist in a proportion such that each contributes 50% of the total complement-fixing activity. On storage and on

more violent treatment disintegration of the large component takes place with decrease of infectivity, and a relatively higher proportion of complement-fixing activity appears in the small component fraction.

Heat treatment produces this effect within a few minutes. The intermediate component appears in sedimented larger material. Deposits from the original virus suspension resuspended and recentrifuged yield supernatants which have considerable complement-fixing activity. It would appear that this intermediate component is shed from the surface of the large particle, although complete disintegration of a small proportion of the total large particle present, might account for the results. In addition to the criterion of size, the components may be differentiated by serological methods. The large component is almost completely type specific in complement-fixation tests, while the small component is almost completely without type specificity. The intermediate component has a serological specificity which is intermediate between that of the large and small materials. When, however, the large particle is disintegrated by less gentle means, such as heating, the small component is not type specific. A possible hypothesis is that all the small component contributing to the structure of the large, is originally type specific, but that it is denatured on storage or by heat treatment, to yield small component of the more typical poor specificity. One interesting point here, to which I shall refer later, is that the small components of two sub-types, e.g. two sub-strains of type "O" corresponding in influenza to two sub-strains of type "A" such as A′ and Asian, can be differentiated by serological methods. This is surprising when it is not possible to differentiate sharply between small components derived from two strains of entirely different types (e.g. O and A). The relationship between the large component and the small component has recently been demonstrated in a new and very pretty way by Brown and Crick (1957). First, when virus and serum diffuse towards each other in agar gels, two lines are formed. These correspond to the precipitin zone of the large 20 m$\mu$ particle, and the small 7 m$\mu$ particle, for if the separate fractions are similarly diffused towards each other, adjacent to the test on unfractionated virus, the lines merge with the appropriate line in the double line of the unfractionated material. Tests with the separated components of the virus system seemed at first to show an anomaly between the gel diffusion result and the result of complement-fixation tests, for in gel diffusion tests small component gave a line only with homotypic serum, and not with heterotypic also, as might have been expected from the complement-fixation test. When an agar gel diffusion test was carried out with small component, to which had been added heterotypic serum, no line was formed, indicating combination of small component and heterotypic antibody. With the large component, addition of heterotypic serum had no effect on the production of a line. A simple expression of the result is to say that the combination of small component with homotypic antibody is precipitating and with heterotypic it is not. Brown and Crick (1958) have also been able to demonstrate the heat disintegration of virus by means of agar gel tests. They have also obtained indication of probable existence of two separate antibodies to the large and small component respectively in antiviral sera. Further analysis of this kind should be most fruitful. It is interesting to note that in published pictures of myxoma virus reacting with its anti-sera in this way, three lines have been observed, and in the case of swine fever, two lines (Mansi, 1957).

The work which is most directly comparable with our own on foot-and-mouth disease is that of Schäfer (1957) on fowl plague virus and of the South African group, Kipps *et al.* (1957) on poliomyelitis, rabies and a number of veterinary viruses indigenous to South Africa. Comparison of the findings of these workers with those on foot-and-mouth disease is interesting. Schäfer and Munk (1952) earlier differentiated two particles, the virus and the soluble antigen. In later work Schäfer obtained from a purified elementary body suspension (particles of 70–80 m$\mu$) two other small particles, by shaking the elementary bodies with ether. The two particles were the 30 m$\mu$ hæmagglutinin, and the smaller g-antigen, the bound ("gebunden") antigen, with a diameter of 10–15 m$\mu$. The hæmagglutinin is similar in properties to the elementary particle except that it has no infectivity. Both the hæmagglutinin and the virus particle are precipitated by anti-viral and anti-hæmagglutinin in rabbit sera. The g-antigen on the other hand gives no precipitation with anti-viral or anti-hæmagglutinin in mouse serum or with F.M.1 influenza serum. The s-antigen, that is the soluble antigen found in the original material, has similar serological properties to the g-antigen. Schäfer suggests that the g-antigen is located inside the particle, for no antibody is formed against the g-antigen when whole virus is inoculated into rabbits in which the virus does not multiply. In foot-and-mouth disease the small antigen liberated from the large particle would seem to be on the outside of the particle, since it is readily liberated. Damage by heat, probably not unlike ether treatment, leads to loss of specificity. It may be that some of the apparent identity of g and s-antigen in Schäfer's work is due to the damage to the g-antigen during its preparation. Certainly the comparison is closest

between the s-antigen of Schäfer, and the small complement-fixing component present in untreated virus suspensions in foot-and-mouth disease. There therefore seems to be a distinction between the small component derived from virus particles and those occurring naturally in the tissues. This is in spite of a marked similarity in the size of the material, and one would be inclined to consider that the dissimilarity in property was due to damage to the small antigen derived from the virus in splitting it from the virus, were it not for one observation in influenza by Ada (1957). He has differentiated between the disintegration soluble complement-fixing activity, that is the complement-fixing activity of the antigens of Schäfer's g-type, and those derived from the tissue, that is Schäfer's s-type. The former contains 5·3% of R.N.A. and the latter only 0·7% R.N.A.

The work of Kipps *et al.* (1957) ranges over a number of viruses. They describe the separation of soluble antigen from infective particle in poliomyelitis. The distribution of complement-fixing activity between supernatant and deposit of centrifuged suspensions of the virus in mouse brain was about 8–1 compared with 1–1 in our experience of foot-and-mouth disease. A further difference was that disintegration of the large particle in their case by drying, produced units of 10–12 mμ diameter with no release of soluble antigen. It would be interesting to have data on the specificity of the two particles in poliomyelitis since it has been shown that the specificity of the virus in complement-fixation tests is decreased by heating at 56° in a manner similar to that which has been associated with foot-and-mouth disease virus. If the South African workers are correct in their assumption that the large particle contributes little to the complement-fixing activity, the loss of specificity must be due to degradation of the small particle and not to disintegration of the large. In bluetongue and African horse sickness, the same workers have made studies of specificity of the components. These have been limited to the finding that the soluble antigen is relatively of low specificity. In general it has been the custom, as in the work of McIntosh (1956), to use the neutralization test as an index of specificity of the strains of the virus of African horse sickness and bluetongue. In foot-and-mouth disease, of course, neutralization tests and complement-fixation tests have given quantitatively similar data over a large number of subtype strains. The differentiation of type also gives a similar picture whether it is observed by complement fixation or serum neutralization.

The virus of influenza was the second in which soluble antigen was described. In the twenty years since that event the relationship between the active particles concerned has been built up into a structural hypothesis far beyond anything which is yet possible with the smaller viruses. Several points of difference stand out between influenza and the viruses we have been considering. The serological specificity of soluble antigen is type specific only, while the large particle is strain specific. This is in agreement with observations on foot-and-mouth disease, but, in addition, for foot-and-mouth disease there is the curious observation that although the small particles of two different types are difficult to distinguish, it is still possible to differentiate the small particles derived from two different strains of virus, just as effectively using strain specific antisera, as it is to differentiate the unfractionated virus. Sonic vibration removed some soluble antigen from the virus of influenza, but complete disintegration with loss of infectivity resulted in liberation of more soluble antigen. The implication is that, as with foot-and-mouth disease, there are small particles more or less closely bound to the surface of the large particle. These can be removed without loss of infectivity whilst in the deeper structure there is perhaps a reserve of soluble antigen which is liberated only on disintegration. There has been a tendency to regard the soluble antigen as the basic unit of virus multiplication. It is possible only to discuss this hypothesis in terms of influenza and some related viruses where there is some good supporting evidence. For other viruses it seems that a great deal more work is required to characterize the so-called soluble antigens, particularly in regard to their properties when they are obtained as a result of various treatments. It seems quite clear that the products which are obtained vary according to the severity of the process by which they are derived from the initial virus suspension. Further work is required also on the study of the physical properties of these materials. It seems clear that some at least of the so-called soluble antigens really consist of complex collections of particles of different size and different chemical composition. Work with the virus of vesicular stomatitis (Bradish, Brooksby and Dillon, 1956) indicated that there were at least four particles of different size in the viral suspensions, and it was almost impossible to delineate sharply the properties of the small particles, since they appeared to exist in variable proportions in different virus suspensions in a size range which it was difficult to separate in the centrifuge. It would not be surprising if this considerable diversity of composition and structure in the various viruses was related to a difference in the role which these small particles play in virus multiplication, structure and disintegration.

The diversity of characteristics of the virus seems to be a suitable place to finish. In

conclusion, it may be conjectured that, although it has not been possible yet to interrelate the two aspects of virology dealt with in this paper, the time is not too distant when each may contribute to the other. Structural changes on modification may yet be beyond our ability to detect, but this detection waits only on progress in this field.

## REFERENCES


ADA, G. L. (1957) In: The Nature of Viruses. Ciba Foundation Symposium. (Eds.: G. E. W. Wolstenholme and E. C. P. Millar.) London; p. 104.

BRADISH, C. J., BROOKSBY, J. B., and DILLON, J. F. (1956) *J. gen. Microbiol.*, **14,** 290.

——, ——, ——, and NORAMBUENA, M. (1952) *Proc. roy. Soc. Ser.* B., **140,** 107.

BROOKSBY, J. B. (1953) In: Nature of Virus Multiplication. (Eds.: P. Fildes and W. E. Van Heyningen.) London; p. 246.

BROTHERSTON, J. G. (1951) *J. comp. Path.*, **61,** 265.

—— (1955) Quart. Res. Rep. E. Afr. vet. Res. Org. 1954 (Oct.).

BROWN, F., and CRICK, J. (1957) *Nature, Lond.*, **179,** 316.

——, —— (1958) Virology. (In press).

BURNET, F. M., and BULL, D. R. (1943) *Aust. J. exp. Biol. med. Sci.*, **21,** 55.

CRICK, F. M. C., and WATSON, J. D. (1956) *Nature, Lond.*, **177,** 473.

——, —— (1957) In: The Nature of Viruses. Ciba Foundation Symposium. (Eds.: G. E. W. Wolstenholme and E. C. P. Millar.) London; p. 5.

DANE, D. S., DICK, G. W. A., CONNOLLY, J. H., FISHER, O. D., and MCKEOWN, F. (1957) *Brit. med. J.*, i, 59.

EDWARDS, J. T. (1949) *Brit. vet. J.*, **106,** 34.

GILLESPIE, J. H. (1954) *Cornell Vet.*, **44,** 425.

HENDERSON, W. M. (1952) *J. Hyg., Camb.*, **50,** 182.

HIRST, G. K. (1947) *J. exp. Med.*, **86,** 357.

KIPPS, A., NAUDÉ, W. DU T., POLSON, A., SELZER, G., and ENDE, M. VAN DEN (1957) In: The Nature of Viruses. Ciba Foundation Symposium. (Eds.: G. E. W. Wolstenholme and E. C. P. Millar.) London; p. 224.

KOPROWSKI, H. (1955) In: Poliomyelitis. W.H.O. Monograph 26. Geneva; p. 335.

MANSI, W. (1957) *J. comp. Path.*, **67,** 297.

MCINTOSH, B. M. (1956) *Onderstepoort J. vet. Res.*, **27,** 165.

NAGEL, H. C. (1937) *Dtsch. tierärztl. Wschr.*, **45,** 624.

NAKAMURA, J., and KURODA, S. (1942) *Jap. J. vet. Sci.*, **4,** 75.

——, FUKUSHO, K., and KURODA, S. (1943) *Jap, J. vet. Sci.*, **5,** 455.

SABIN, A. B. (1955) In: Poliomyelitis. W.H.O. Monograph 26. Geneva; p. 297.

SCHÄFER, W. (1957) In: The Nature of Viruses. Ciba Foundation Symposium. (Eds.: G. E. W. Wolstenholme and E. C. P. Millar). London; p. 91.

——, and MUNK, K. (1952) *Z. Naturf.*, **7b,** 573.

SCHNEIDER, B. (1956) *Mh. Tierheilk.*, **8,** 176.

SKINNER, H. H. (1951) *Proc. R. Soc. Med.*, **44,** 1041.

—— (1954) *Nature, Lond.*, **174,** 1052.

TRAUB, E., and SCHNEIDER, B. (1948) *Dtsch. tierärztl. Wschr.*, **55,** 274.

YOUNG, G. A. (1952) *J. Amer. vet. med. Ass.*, **121,** 394.

# Section of Neurology

President—W. Ritchie Russell, C.B.E., M.D., D.Sc., F.R.C.P.

[*October* 3, 1957]

## The Physiology of Memory

### PRESIDENT'S ADDRESS

By W. Ritchie Russell, C.B.E., M.D., D.Sc., F.R.C.P.

It is hard to realize that only 200 years ago the brain was still thought by our forefathers to consist of a concoction of spirits which might be pure and tranquil, or riotous and evil. It was no wonder that the highly complex human mind was considered to be a thing apart from this squashy organ. During the past 100 years, however, the astonishing complexity of the central nervous system (C.N.S.) has been slowly unfolded until its structural mysteries have become even harder to understand than say the so-called mental processes of our friends! This state of affairs has inevitably caused a revolution in man's attitude to his C.N.S., and indeed there seems to be little limit to what this structure might be capable of.

As examples of the changing concepts regarding the C.N.S., I propose to discuss briefly a few of the physiological processes which seem to be concerned with memory, but I should first point out that a certain amount of speculation is unavoidable in discussing a subject about which we know so little.

There seem to be two particularly important aspects of the development of C.N.S. patterns, to which I should like to refer. There is first the apparently fundamental tendency for nerve cells to repeat patterns of activity, so that all reactions have a strong tendency to form arrangements which are repeated whenever possible, and around which more elaborate responses are built. The tendency to repeat seems to be one of the most powerful features of all nervous system activity. The physiological basis for this is of great interest, and will be considered later.

The activity of the mature C.N.S. usually falls into well-worn patterns which have formed during the years of development. These furrows of habit become first, ruts to guide and then, chains which control our responses to a greater or lesser degree. These bonds of habit affect simple motor performances very strongly so that our very movements assume a unique character: thus the constancy of our handwriting must be a source of wonder and thankfulness to every banker. This capacity to repeat a previous response is clearly an essential part of the physiology of memory.

The second of these particularly important aspects is the capacity of all forms of animal life to encourage or discourage a response according to whether it appears to be advantageous or disadvantageous to the organism.

In the highly developed C.N.S. of man and mammals this system is probably thrown into action at birth by powerful afferents from the infant's viscera and orifices, especially the mouth, but this is soon elaborated into an ever more complex system in which fronto-hypothalamic mechanisms play an important part. This might be referred to as a *personal reaction* in which what we call *feeling* becomes a prominent feature. This reaction also shows a strong tendency to repetition, and is clearly concerned with the development of the individual feeling response to circumstances.

Although the studies of Freud and his followers have sometimes strayed from the path of reality, yet their insistence on the importance of the earliest infantile responses in relation to the development of future characteristics of the individual, is in accord with the background on which what I have called the personal response seems to develop. This appears to me to provide a powerful link between psychology and physiology, which are still somewhat artificially separated from each other. Certainly this personal reaction

to events itself forms patterns of response, or habits which seem to lay the foundations on which the individual's characteristics are formed.

From the point of view of memory itself, this personal response is of special importance as it helps to ensure that items which it considers to be advantageous are remembered, and of course, from the point of view of learning, the wish to learn is vital, and presumably represents the personal reaction to what is unknown.

Here then are two striking features of C.N.S. activity—the urge to repeat and the capacity to facilitate what is advantageous—and it is especially with the first of these that we are concerned in studying memory.

Ever since anatomists (including Ramon y Cajal) discovered that the C.N.S. is built up of neurones, it has been realized that much must depend on the properties of these units, and the manner by which they form synaptic connexions with each other.

It is therefore of great importance from the point of view of our subject that neurophysiologists have, in recent years, demonstrated that transmission from one cell to another is greatly augmented if there has been preceding activity across this connexion. This effect has been shown by experiment to operate exclusively in the presynaptic apparatus (Eccles, 1957; Granit, 1955). This is evidence regarding a neuronal mechanism which can be correlated with the tendency to repeat which permeates all levels of C.N.S. activity.

## Physiological Mechanism of the Ability to Repeat

In attempting to provide a working hypothesis for the most primitive type of memory—the simple repetition of a reaction—we must appreciate that most cells of the C.N.S. are in a state of constant, if somewhat random, activity in which they discharge spontaneously day and night, often at a high rate along the processes which communicate with other nerve cells (Young, 1946). The afferent stimuli which lead to reaction or action, are not therefore thrown into a mechanism which is idly waiting for something to do, but into one which is already busily occupied. It is equally evident, however, that this complicated neuronal activity is extremely sensitive to outside (afferent) influences. Apparently the neuronal pool can be alerted to make responses which take priority over spontaneous activity, but a trained and attentive C.N.S. will direct new arrivals into well-established channels, so that if a certain response has in the past followed a given experience, there is every likelihood that this response will be repeated in the future to the same stimulus, until it acquires a remarkable degree of constancy and automaticity.

Even the simplest C.N.S. response involves a vast number of repetitions in the physiological sense; thus the cells involved may perhaps discharge at the rate of 500 per second for several seconds during the height of the response, and may then settle down to relatively slow spontaneous 40–50 per second which causes no overt effect and yet may play a part in preserving the pattern of response.

## Simple Learning Processes

The development of constancy in this response constitutes a learning process and in many instances a response seems to be learned quite quickly. Apart from brief interruptions, the neurones concerned continue their spontaneous discharges, and it seems natural to consider that *these spontaneous discharges tend to be directed into the paths opened up by the learned response.* Having learned to walk or cycle one never forgets, not because some pattern is hidden away in a mysterious memory centre, but because the spontaneous activity of the neurones concerned maintains and indeed strengthens the once-established pattern of the response. This mechanism is so remarkably effective that the task once learned may be executed better after an interval of apparent neglect, and the suggestion made is that the C.N.S. maintains what is learned by spontaneous discharges of the cells which are "exercising" as it were, through the neuronal pattern established when the skill was first acquired (Russell, 1948).

In other words the establishment of the original pattern for the response also established the direction in which the spontaneously occurring activity would tend to flow, and this in its turn would strengthen itself and thus maintain and consolidate the capacity of the organism to repeat, retain and strengthen the skill.

In this sense therefore and unbeknown to the individual, the C.N.S. practises its learned skills and other memories throughout life.

This raises interesting possibilities for there may well be circumstances in which the unconscious activity of the C.N.S. provides a more effective form of training than does actual practice; and, of course, it is intriguing to speculate on the part which this mechanism may

olay in assisting the mental clarification which often results from putting aside a complicated problem from one's conscious thought for a few days or hours.

Here, however, I am jumping to the conclusion that the memory of a physical task and of a so-called mental problem are basically dependent on the same physiological mechanisms.

### Structural Changes at Synapses

The physiological mechanism whereby an active synapse becomes facilitated for future use is not fully understood, but there is some evidence to suggest that physical changes may play a part. Thus the synaptic knobs on the surface of anterior horn cells may, in response to great activity, get larger (Eccles, 1953), and recent work raises some interesting possibilities about a somewhat similar process in the inter-fibre synapses of the cortex. For long there has been something of a mystery about inter-fibre transmission in the cortex but studies described by Bok (1956) suggest a plausible explanation. He has found that 90% of the cerebral cortex consists of spaces which separate nerve cells, glial cells and blood vessels. In this space an immense number of nerve fibres cross each other in various directions, and this fibre density remains much the same in different layers of the cortex, and indeed as between man and animals. The distance which separates crossing nerve fibres is also remarkably constant, and this separation of one fibre from another is apparently maintained by a foam-like structure of spheres whose diameter is about 5$\mu$. It is suggested therefore that fibre synapses depend partly just on the distance which separates fibres from each other. In other words close crossings are facilitated synapses.

A further clue to this is probably provided by a study of the spikes (gemmuli) which appear on the dendrites of cortical pyramidal-type cells. Bok has demonstrated that the gemmuli on a dendrite are, on the whole, separated from each other by a regular distance (2·5$\mu$). This corresponds to the distance apart of the points where crossing fibres would come in close contact with the dendrites on the above arrangement of foam particles. It seems therefore that every spike on the dendrites may become a close-crossing synapse. Further the development of the gemmuli greatly enhances the effectiveness of the close-crossing synapse by further approximating the crossing fibres. Indeed this increase in size of the fibre at the point of crossing almost (and perhaps entirely) eliminates the space between the crossing fibres. In this simple way the effectiveness of the synapse receives the maximum enhancement.

The development of these gemmuli is presumably a physical change which results from the activity of the synapses concerned, and plays an important part in enhancing their activity. Tremendous multiplication of these occurs during first two years of life. The crossing at the gemmuli suggests a very firmly-established type of close-crossing synapse, but it may be assumed that simpler mechanisms of enhancement occur without the formation of so much physical change.

In any case the available physiological knowledge suggests that patterns of behaviour depend on the establishment of functional changes at the synapses and not in the cell body. When we laboriously learn to walk we establish a pattern of reaction which probably differs only in the degree of complexity from the higher forms of memory. This conception is important for it suggests that memory, far from depending on passive changes in nerve cells, is a very active process, and becomes lost only when the neurones concerned cease to discharge along the pathways once facilitated. The student of the brain must often be astounded by the complexity of function involved in the simplest mental process, and yet the complexity of the mechanisms involved in voluntary movement is equally astonishing. It is safe to say that if we could understand fully the mechanisms involved in learning the patterns of voluntary motor activity we would be more than half-way towards understanding the physiology of thought processes.

There has sometimes been a tendency to look for some special area of the brain into which all memories could be filed, but this has always seemed to me to be a highly improbable conception. Thus the memory of a physical skill must surely be contained in all parts and levels of the C.N.S. which influence the performance of the skill. Memory of a skill and capacity to repeat it are to some extent one and the same, and the same principle should apply to the higher forms of memory.

Another quality of C.N.S. activity is its capacity to effect a series of responses in a certain order and sequence, and this is a very constant feature of learned responses. From the physiological point of view various phenomena have been demonstrated which introduce delays from one cell to another, but apart from this, the time and sequence patterns of these reactions are little understood. In general, however, there is a striking tendency in all C.N.S. activity for one response to be followed by another, and indeed many motor

performances of skill depend almost entirely on reactions which can only occur as a sequence to the first action.

There is also the capacity to co-ordinate one motor memory with another: thus a bandsman remembers both how to walk and how at the same time to play the drum. Presumably our capacity to associate one memory with another at a high level differs again only in complexity with such sensorimotor reactions.

A poem or a piece of music is most easily remembered as a sequence which follows the beginning, and in the highest forms of memory, those with exceptional power in this direction depend largely on a vast capacity of associating memories with each other this seems to represent a vastly complex type of the simpler ability for one motor reaction to be followed by another.

The recognition of the familiar is an important aspect of memory. A familiar or unfamiliar sight must project in the same pattern on the visual cortex. Most of those patterns are promptly extinguished, but if some attention is aroused, then the familiar is quickly recognized, presumably because the pattern is entering facilitated circuits. Familiar patterns often stimulate a personal feeling of contentment. On the other hand a highly unfamiliar pattern of sound or sight often acts as a strongly alerting reaction with the personal response of fear. These interesting facets of memory are of special interest, as feeling responses to the familiar and unfamiliar may be abolished in animals by certain temporal lobe excisions.

## Phantom Limbs

The study of phantom limbs in amputees provides some interesting examples of sensorimotor memory. It is natural that the brain should interpret sensations from the cut nerves as originating in the missing limb. The brain has been trained for many years to interpret these sensations in this way. But if a child should lose a limb in the early months of life, no phantom will develop as the opposite parietal lobe has not yet developed a strong association with the limb.

In many amputees the phantom sensations disappear after a few months. In some, however, after an interval of perhaps twenty years, a painful condition develops in the stump, and once again severe pains are experienced in the phantom. This is a remarkable example of the preservation of an entirely neglected sensorimotor memory. Even more remarkable is that the phantom pain may revive memory of a pain which was felt severely before the limb was amputated (Russell and Spalding, 1950).

In this connexion it is of interest to note that wounds of the parietal lobe of the brain may abolish appreciation of the position of contralateral limbs in relation to the rest of the body (Brain, 1950)—the so-called loss of body image; and in contrast an epileptic aura originating in the parietal lobe may occasionally be a strong phantom sensation in an opposite limb—a forceful distortion of the body image mechanism (Russell, 1951).

## The Hippocampal System

There is plenty of evidence to indicate that the hippocampal system is very much involved in this mechanism of memory and recognition of the familiar. Removal of the hippocampus and anterior temporal lobes on both sides causes a remarkable state as Scoville and Milner report (1957). They found that in patients so treated the incidents of daily life were forgotten as quickly as they occurred. Yet details of childhood were well remembered. A somewhat similar result follows disease of the region of the mammillary bodies as in Korsakoff's psychosis, and these bodies form an essential link in the hippocampal system.

Of special interest in this connexion are the temporal-lobe fits which cause an intense sense of familiarity for in this type of focal fit all that is happening seems as if it had happened in the same way before. No other part of the brain stimulates a sense of intense familiarity or *déjà vu* sensation and it seems likely that the hippocampus is concerned. The focal epileptic fit often caricatures the function of the part of the brain affected so that the occurrence of such fits from the temporal lobe confirms the importance of this region for the physiological reaction which is needed to facilitate neuronal patterns in such a way as to enable an event to be remembered, and to become familiar.

In Korsakoff's syndrome also there is a remarkable dissociation between remote memory and remembering of current events. For it seems as though these remote memories were learned originally with the assistance of a mechanism now out of order, and new learning becomes impossible, though the earlier results are still available. The mechanism that is now out of order was probably the one used to establish originally what is preserved.

This separation of function is also seen in many other states of disordered brain function such, for example, as occur during recovery from concussion. It seems that the mechanism of adding to memories—the recording of events—is more complex and relatively vulnerable, while what was added to memory before the disorder of the mechanism remains relatively secure.

In Korsakoff's syndrome there is plenty of evidence to indicate that an important link in the hippocampal system is broken, for the corpora mammillaria show gross changes and their relations with the hippocampus are so close that their inactivation might be expected to put the system out of action.

It is not unduly fanciful, therefore, to consider that the hippocampus plays an important part in both memory and learning processes. It certainly has free connexions with all parts of the cortex, and such a major contribution to thought and behaviour would give it a role well worthy of its great development in man and animals. Yet, although concerned with learning, it probably plays little part in actually storing what has been learned. Its action on the cortical mechanism concerned with visual memory, for example, must be a boosting, feed-back or re-playing mechanism. And, in addition, it might contribute to the essential stimulation of associated ideas and feelings which are so important in consolidating memories.

It is of great interest to study those parts of the brain from which formed visual hallucinations may occur as part of an epileptic process. Dr. Whitty and I (Russell and Whitty, 1955) found that these might occur not only in temporal lobe injuries but also in parieto-occipital lesions. This suggests that both sites are intimately concerned with visual memory; the parieto-occipital region being the region where the main pattern of facilitated circuits lies, and the temporal lobe being concerned perhaps through the hippocampal system in boosting these mechanisms.

These posterior lesions may cause hallucinations of remembered scenes as described by Robinson and Watt (1947), and from wounds further forward in the parietal lobe there may be, as already mentioned, phantom sensations (Russell, 1951) which represent a distortion of the memory of the position of the contralateral limbs in relation to the body image. The disappearance of visual memory and of dreaming (Humphrey and Zangwill, 1951) have been reported in destructive lesions of this part of the brain.

Study of the effects of head injury or senile changes on memory also demonstrate the special vulnerability of recent memories, and indeed it seems that many memories are strengthened with the passage of time regardless of their importance to the individual. This is what one would expect if memory depends on synaptic facilitation of neuronal circuits, which continue to strengthen themselves whether we are interested in them or not.

## Hallucinations

Hallucinations provide an interesting study of a disordered memory mechanism. Visual hallucinations are generally of objects which are recognized by virtue of previously acquired knowledge. Thus in delirium tremens the victim is in no doubt as to the type of animals he sees for their appearances are quite familiar to him.

Many individuals with a strong visual sense can develop a special capacity to see things in their mind's eye. This is a simple physiological phenomenon, which may result in artistic productions. Some forms of modern art seem to depend on a cultivated capacity for hallucinatory phenomena to occur in relation to certain feelings. The idea, however, that these haphazard visual images are worth reproducing as works of art seems to me to be based on a misconception of their physiological significance. The artist seems to think that these phenomena are emerging from some unique storehouse of his personal genius, but, on the contrary, the available evidence suggests more that they represent a confused glimpse of fragmentary repetitions of previous thought or reactions.

Hallucinations during illness are likely to be based on remote memories around which there were at one time strong emotional feelings. Thus a woman with delirium tremens may scream with terror at pink mice on the walls, and yet it may have been many years previously that she last experienced an emotional reaction of fear in relation to mice.

A middle-aged doctor while experiencing an infective disease causing an encephalopathy developed some hallucinations which were, in general, of featureless buildings, but somewhat to his surprise, these hallucinations included an illustration from an anatomy textbook which had interested him greatly when he was a young medical student many years previously.

Of special interest are hallucinations of self (Dewhurst and Pearson, 1955), as they tend to be of head and shoulders as would often have been seen in a mirror, and no doubt this

appearance has also at one time, perhaps many years previously, aroused an undue amount of interest in the person concerned.

The various visual and auditory memories with their associated emotional responses are contained chiefly in different areas of the cerebral hemispheres, but during hallucinosis the stimulus to uncontrolled activity seems to come from some central system which plays back excessively to the regions such as the parieto-occipital region which is so much concerned with visual memory. The actual hallucinations which appear must depend on many chance factors just as occurs in dreams which, no doubt, make use of a similar mechanism. Indeed hallucinations and dreams are similar in many respects.

The traumatic amnesias are of great interest in relation to our subject (Russell and Nathan, 1946). It is now generally agreed that the concussive effect of a closed head injury is a direct physical disturbance of neuronal function, which leads to a paralysis of brain function.

The gradual recovery of mental processes after head injury provides a vivid picture of the return of first, the less complex, and last, the more complex mechanisms. In this connexion it is informative to realize that current events are not remembered until the recovery of brain function is more or less complete.

During recovery of consciousness it is of special interest to study the commonly occurring phenomenon of shrinkage in the retrograde amnesia. This is best observed in severe cases with slow recovery over a period of several days or weeks. During such recovery recent memories may be so severely lost that the patient thinks himself to be some years younger, and expects the environment and date to be appropriate for that age. Further, if the injury is of such severity as to cause some permanent loss of things previously learned, then this loss is most likely to affect recently acquired knowledge or skills.

Thus in all traumatic or disease processes of the brain there is evidence that recently acquired memories are most vulnerable, while remote memories are often remarkably resistant to disease or trauma. This is therefore a fundamental feature of cerebral dissolution, and can, I think, be explained on the basis put forward that memories depend on synaptic facilitations which strengthen automatically as time passes. Early childhood memories may be relatively indelible for the further reason that the physical changes consequent on prolonged facilitation at a synapse no doubt develop most readily in the child's brain.

The occurrence almost invariably of a short period of retrograde amnesia after recovering from concussion is of course of very special importance, for it clearly indicates that the establishment of a memory, even of the most vivid and emotionally tinged type, requires a period of one or two seconds of normal brain activity, if it is to survive the paralysing effect of concussion. This seems to be a very short time but one second is quite a long time from the neurophysiological point of view.

Of special interest are the occasional visual hallucinations soon after recovering consciousness after head injury. These may be concerned with dramatic events which fall within the period of retrograde amnesia (Russell, 1935; Russell and Nathan, 1946). These visions are only half memories and are soon lost. There is no associated feeling in regard to them, and this can presumably be correlated with their not having been played on by hippocampal and emotional mechanisms.

We might here almost guess that the hippocampal system has to play back to the parieto-occipital region for a period of seconds before even a vivid visual experience can be established as a faint memory. If the cells concerned discharge at the rate of up to 500 per second one gets a rough estimate of how long this effect requires to come through.

It is, of course, even more remarkable that this mechanism of remembering is so efficient that many victims of moderately severe head injuries remember clearly the events which occurred say 10 seconds before the injury. This suggests that the neuronal activity even during the period of traumatic confusion continues to strengthen its memories through its spontaneous activity.

The time factor is only one of many which are concerned with memory. For example, the factor of attention seems to be perhaps the most important of all, for afferents pouring in from the special senses seem to be extinguished automatically, unless they arouse what Pavlov called the "What is it?" reaction.

Further the gradual strengthening of a memory with the passage of time depends on its remaining relatively isolated, and not becoming confused by a large number of closely similar memories, as I have previously pointed out (Russell, 1948). An experience is not so easily recalled when it ceases to be unique, but becomes confused by scores of very similar memories.

In conclusion, I can only draw a somewhat terrifying picture of thousands of millions of nerve cells all discharging throughout life at high speed, by day and by night to maintain the synaptic patterns on which our memories depend. The very thought of such a mechanism must fill us with a feeling of incredulity. Certainly it makes one tired to think of, but then mental tiredness is itself a remarkable phenomenon.

If our memories are, in fact, facilitated neuronal circuits which never rest, how can we prevent them from constantly disturbing our lives? Thus if the memory of how to swim involves circuits which never rest, why are we not constantly waving our arms and legs around in response to this constant activity?

The answer may lie in a study of what happens to nearly all impulses reaching the nervous system, for it has become quite evident that only a minute fraction of say visual afferents from the retina are "seen" at all. It seems that nearly all afferents to the C.N.S. are immediately extinguished by a process of inhibition. How can this come about? The neurophysiologist will naturally think of the recently described recurrent twigs from the axons of pyramidal cells which have a powerful influence on an inhibitory system connected with the cells described by Renshaw (1946). It is thus quite possible that every pyramidal type of cell has its own cut-out system. In this way it becomes conceivable that our memory neuronal patterns can remain constantly active without reaching what we call consciousness.

What enables us to think of one of our memories or to remember something we see or hear, seems to depend on some general alerting process, and we might here even use the term centrencephalic system as visualized by Penfield.

A friend of mine, a research worker of exceptional originality, told me that if a ticking clock stopped while he was engaged in some mental activity unrelated to the clock, he realized that something had happened and his first memory was of the clock ticking before it had stopped, and he estimated that he would remember about 5 seconds of ticking before it ceased.

Thus it seems that the change from ticking to non-ticking alerted the hearing side of the brain, and that this enabled the memory of recent ticks to be recaptured before they were extinguished like the memory of all other ticks. It is well known that those in charge of running machinery of any kind are alerted by any change in the running sounds.

Also if one suddenly starts listening to what someone is saying, it may be possible to recapture the word or two before alerting began, usually not enough to avoid getting into trouble for not listening to what is being said.

In any case it seems evident that we rely on nearly all the afferents arriving at the C.N.S. being promptly extinguished, and one might even guess that a disturbance of this balance might play a part in the ætiology of traumatic epilepsy.

It must be obvious from this brief address that there are more unsolved than solved problems. Yet from time to time we must try to take another step forward towards unravelling the mysteries of cerebral mechanisms.

## REFERENCES


BOK, S. T. (1956) The synapses in the cerebral cortex. Proceedings of the First International Meeting of Neurologists. Amsterdam.

BRAIN. W. R. (1950) *Brain*, **73**, 465.

DEWHURST, K., and PEARSON, J. (1955) *J. Neurol. Psychiat.*, **18**, 53.

ECCLES, J. C. (1953) The Neurophysiological Basis of Mind. Oxford.

GRANIT, R. (1955) Receptors and Sensory Perception. New Haven, Conn.

HUMPHREY, M. E., and ZANGWILL, O. L. (1951) *J. Neurol. Psychiat.*, **14**, 322.

RENSHAW, B. (1946) *J. Neurophysiol.*, **9**, 191.

ROBINSON, P. K., and WATT, A. C. (1947) *Brain*, **70**, 440.

RUSSELL, W. R. (1935) *Lancet*, ii, 762.

—— (1948) *Quart. J. Psychol.*, **1**, 1.

——, and NATHAN, P. (1946) *Brain*, **69**, 280.

—— (1951) *Proc. R. Soc. Med.*, **44**, 341.

——, and SPALDING, J. M. K. (1950) *Lancet*, ii, 68.

——, and WHITTY, C. W. M. (1955) *J. Neurol. Psychiat.*, **18**, 79.

SCOVILLE, W. B., and MILNER, B. (1957) *J. Neurol. Psychiat.*, **20**, 11.

YOUNG, J. Z. (1946) Patterns of Substance and Activity in the Nervous System. London.

[*November* 7, 1957]

## Meeting at the National Hospital for Nervous Diseases, Queen Square, London

The following cases were shown:

**Wasting of Tongue in a Child.**—Dr. F. Clifford Rose (for Dr. M. J. McArdle).

**"Hyperkalæmic" Type of Familial Periodic Paralysis.**—Dr. Brian McArdle.

**Chiasmal Lesion Following Successfully Treated Tuberculous Meningitis.**—Dr. C. J. Earl (for Dr. M. J. McArdle).

**Case Illustrating the Use of Leksell's Stereotaxic Apparatus: Parkinson's Disease Treated by Thermo-Coagulation of the Globus Pallidus.**—Dr. J. Hamilton Paterson and Mr. L. S. Walsh.

**Post-influenzal Encephalitis.**—Dr. Peter Croft (for Dr. R. A. Henson).

**Hereditary Ataxia with Disordered Eye Movements.**—Dr. Peter Ebeling (for Dr. E. Arnold Carmichael).

**Hepato-lenticular Degeneration.**—Lt. T. D. R. Hockaday (for Dr. W. Ritchie Russell).

**Orbital Venous Angioma.**—Dr. M. M. Schechter (for Dr. S. P. Meadows).

# Section of Ophthalmology

President—J. R. WHEELER, F.R.C.S.Ed.

[*October* 10, 1957]

## The Ageing Eye

### PRESIDENT'S ADDRESS

By J. R. WHEELER, F.R.C.S.Ed.
*Belfast*

THE last fifty years have seen tremendous advances in all branches of science, and in the science of medicine these advances might be termed spectacular. Insulin, liver therapy, sulphonamides, antibiotics, corticosteroids and hypotensive drugs, to mention but a few, all help to prolong the lives of the population, so one finds a much larger proportion of people living beyond the Biblical span of three score years and ten.

It is interesting to observe the estimated population of persons over 65 years of age during the next forty years as shown in the Registrar-General's returns. One notices that a very considerable increase of longevity is predicted, and that in the 85 and over group the number of persons alive will be more than double what it is to-day.

ENGLAND AND WALES

Table Population, Projections from mid-1955 by Sex and Age. Prepared by Government Actuary's Department in consultation with the General Register Office

*Figures in Thousands*

| *Age* | 1955 | 1975 | 1995 |
|---|---|---|---|
| 65 | M. 785 | M. 1,154 | M. 1,066 |
| | F. 1,082 | F. 1,396 | F. 1,255 |
| | 1,867 | 2,550 | 2,321 |
| 75 | M. 385 | M. 484 | M. 572 |
| | F. 617 | F. 828 | F. 874 |
| | 1,002 | 1,312 | 1,446 |
| 85 and over | M. 78 | M. 97 | M. 159 |
| | F. 167 | F. 270 | F. 389 |
| | 245 | 367 | 548 |

Man is probably at the peak point of physical fitness in the mid-twenty period—it is at this age that one will find the majority of Olympic sprint champions. More maturity, however, is required for long distance races which put a long-sustained strain on the cardiovascular system.

Perhaps the first positive sign we get that the process of ageing is upon us is the onset of presbyopia. Then the onset of the post-reproductive age period may bring with it some degree of rheumatism or arthritis.

Most degenerative conditions are secondary to a less efficient blood supply through less elastic arteries—it would seem that tissues have a time scale beyond which either no replacement takes place or the replacement takes place with increased lack of efficiency. Then there is a group of conditions with the age of onset under genetic control—severe vascular hypertension, myocardial infarction, &c. Finally the older age groups have probably been exposed to a larger series of traumatic insults from injury or disease and so are more liable to suffer from their cumulative experiences.

To try to find out the true position of the ageing eye, I have surveyed three groups of persons who have passed the usual, if arbitrary, retiring age of 65 years.

*First:* The registered blind persons in Northern Ireland over 65 years of age.
*Second:* Over 250 inmates of a geriatric unit.
*Third:* 138 inmates of an old people's home.

## Registered Blind Persons

Before reviewing the data contained in the blind registration certificates obtained from the Ministry of Health in Northern Ireland there are three points to which I would like to draw attention:

(1) All patients were examined by an ophthalmic specialist.

(2) The official definition of a blind person under the Act is one who is unable to perform any work for which eyesight is essential. This is a good practical definition, but obviously somewhat loose and open to slight variations. One finds in practice that perhaps 15% of these certified blind persons are able to look after themselves and get about in their own known surroundings.

(3) To qualify for a blind pension one's income must be below a certain figure. The total list of registered blind persons shows that less than 50% draw a pension.

### Causes of Blindness

(in persons of 65 years and over)

| | % | | % |
|---|---|---|---|
| Cataract .. .. | 31·43 | Corneal .. .. | 5·48 |
| Glaucoma .. .. | 19·15 | Old trachoma .. | 1·28 |
| Myopia .. .. | 10·51 | Optic atrophy .. | 3·60 |
| Macular lesions .. | 6·76 | Retinal detachment | 1·28 |
| Vascular .. .. | 4·74 | Congenital .. | 1·26 |
| Choroidal .. | 3·88 | Disease of C.N.S. .. | 0·86 |
| Iritis and cyclitis .. | 6·62 | Trauma .. .. | 0·43 |
| | | Unclassified .. | 2·72 |
| | 83·09% | | 16·91% |

Reviewing the data available from the Northern Ireland Ministry of Health I find that out of a population of 1,394,000 people 2,600 were certified as blind, or one person in every 536. The data from England and Wales for the same period shows that one person in every 485 is certified as blind.

Of the 2,600 blind in Northern Ireland 65% are 65 years of age and over (the age group being examined). The number of cases of cataract is 31%, glaucoma 19%, and a group which might be termed chorio-retinal irrigation lesions, 15%. The other main lesions are the end-results of inflammatory reactions of the structures forming the anterior segment of the eye, which, when one includes old trachoma cases, stand at 13%. These lesions, plus the cases of high myopia with fundus defects, form the major causes of blindness in the 65 and over age group.

Examination of the blind certificates shows that the great majority of the cataract cases have not even sought medical treatment. Why this state of affairs?—after all, the results of surgery to-day are very good. Gone are the days when one had to wait until the cataract was mature before operating. I tell my students that when the patient's vision is such that he is unable to carry on his work, then it is the surgeon's duty to operate. Unilateral cataracts should be operated upon at the patient's convenience as it gives an increased visual field and also a good "reserve" eye. With advancing years the patient's general health cannot be expected to be perfect—if, however, it is reasonably good, operation is worth trying. There is so much to be gained and so little to lose. Many good results are obtained in patients who are far from 100% fit. In 1953 I read a paper at the Oxford Ophthalmological Congress analysing 114 consecutive cases of cataract I had operated upon. 67% got 6/12 or better vision, while in a further 23% of cases vision was 6/60 or better. Could not this good prognosis which modern surgery offers to those affected with advancing lens opacities be made more widely known, so that they might seek our aid at an earlier date?

An analysis of figures shows that townspeople were the worst offenders in not seeking advice—probably individuals with limited or impoverished life experience, especially as regards hospitals—they develop an anxiety neurosis and have a reduced capacity to deal with events. Old people adjust poorly to changes in environment and readily become emotionally upset with new and different situations, especially separation from their families.

### Senile Changes

It has been suggested that senile cataracts may be part of a generalized degenerative process, and, if this is so, persons with senile cataracts would be more predisposed to structural brain changes than other individuals of the same age group. The probable reason for this suggestion is that occasionally following cataract operation the patient becomes mentally upset. This may vary in degree from acute mania to a mild degree of confusion or disorientation.

The first case report of this in English is in the *Medical Times and Gazette* in 1854. An interesting account is given of a man of 65 years with bilateral cataract—"so great was his fright and agitation that he could not be induced to keep quiet enough to allow his eyes to be opened sufficiently for the operation. The procedure had to be postponed for twenty-four hours so that chloroform could be used. On the first post-operative day delirium set in and continued with violence for five days, during which time the head was tossed about in all imaginable positions". The account says he recovered, and three weeks after operation he saw as well as possible after removal of the lens.

Linn (and others) reporting from departments of Psychiatry, Neurology and Ophthalmology of Mount Sinai Hospital, New York City, on 21 unselected patients with bilateral senile cataracts, state that following cataract extraction 62% of cases showed severely disturbed reactions, while 95% showed some alteration in behaviour. Only 3 cases in the series had a normal EEG and a negative amytal test. These figures are obviously far too high for our country but one must remember that they were dealing with a very mixed population, with language difficulties and with bilateral cataracts. This would bear out the general opinion that it was the structural brain changes present prior to the operation that predisposed these patients to the post-operative psychiatric disorders.

Could it be that these senile mental degenerative changes prevent so many patients, with cataract, from coming to hospital to seek advice and treatment? The older the patient the more liable are these brain changes to be present. The longer the darkness and loneliness period, the more liable are these patients to become introspective, so that delusions and anxiety states arise.

Ophthalmic surgeons should try to get these cases to hospital at as early an age as possible and not give them an opportunity to weave a psychosis out of their phobias of becoming blind, lonely and a burden on their families. Now with the Welfare State one might hope that general practitioners, ophthalmic opticians, health visitors, &c., might persuade these people to come to us in hospital as soon as a cataract is suspected—then we could assess their case and tell them when the opportune time for operation might be. If ready for operation make the waiting time as short as possible; if not ready, tell the patient to return on a certain definite date for re-examination. Try and gain their confidence, and assure them that everything possible will be done to restore their vision.

### Glaucoma

Turning to simple glaucoma—that slow but remorselessly progressive lesion which accounts for almost 20% of blindness in the over 65 age group: ten years ago a very cultured Scot (aged 56) came into my consulting room and told me he had got glaucoma, saying that both his father and eldest brother went blind from glaucoma, and both were operated on by a leading Scottish surgeon. He said it appeared that his family reacted badly to operation and so he did not wish to have an operation. He asked me to give him some warning if he was going blind so that he might buy a house with a little garden where he would be able to find his way about and look after his plants. For the last ten years he has faithfully carried out the recognized conservative treatment for glaucoma. When first examined the diagnosis was definite but field contractions slight—ten years later one eye is blind, and the other has 6/6 vision but the field is contracted to within 10 degrees of the fixation spot.

Perhaps this case may show about how long a conscientious patient's sight may survive under conservative measures. I feel, however, that operations on very advanced cases with markedly contracted field have a poor prognosis and give the operation a bad name.

The blind registration certificates show how few of these glaucoma cases had had any operative treatment, or indeed any treatment. If we could get these cases early our operation results would show a much higher percentage of success.

### Sympathetic Ophthalmia

One must remember that to open the eye carries with it a risk of a resulting sympathetic ophthalmia. Sorsby points out that half of the sympathetic ophthalmia cases causing blindness result from cataract surgery, while 1/6 of this number followed operation for glaucoma. To-day, with the advent of the corticosteroids, antibiotics and sulphonamides

we have a line of treatment which, if pursued energetically, should prevent this dreaded condition materializing. These drugs can have an almost miraculous effect in ordinary cases of iridocyclitis and keratitis, but of course one cannot expect them to undo serious existing established damage. With their early and judicious use, however, blindness resulting from inflammatory lesions of the anterior segment of the eye might possibly be reduced from 13% to almost nil.

### A Geriatric Unit: A Survey of the Eyes of 277 Persons of Age 65 and Over

In this unit cases are classified as follows:

A. Fit, but admitted for social reasons.
B. Frail, ambulant—can get about in hospital but not fit for home.
C. Sick (1) Acute—will eventually recover sufficiently to go home.
(2) Chronic—will not recover sufficiently to go home.
D. Psychiatric—patients admitted because of mental rather than physical inability to look after themselves.
E. Special Groups—e.g. Huntington's chorea, &c.

This group of cases of elderly, frail and infirm persons produced an entirely different ocular pathological picture from what I had expected to find. There are less than 12% with some opacification of the mediæ, and only two cases of glaucoma were found.

The reason for this is probably that people who are simply blind require little or no nursing, and their relatives are encouraged to keep them at home by receiving extra National Assistance. National Assistance is 40/– in the ordinary way, but in the case of a certified blind adult it rises to 60/–, subject to a means test.

The Medical Conditions of a Cross-section of 277 Patients of Age 65 Years and Over

| | | % |
|---|---|---|
| 117 | Cerebrovascular accidents .. .. .. .. .. | 42 |
| 44 | Other cardiovascular lesions .. .. .. .. .. | 16 |
| 61 | Cripples—Rheumatoid arthritis, ununited fractures, &c. .. | 22 |
| 25 | "Social reason" cases .. .. .. .. .. | 9 |
| 30 | Other cases—psychiatric, lesions of C.N.S., neoplasms, &c. | 11 |
| | | 100 |

Analysing the medical condition of my cross-section of patients in this unit I find that 42% of the total had a cerebrovascular lesion, while a further 16% had some other cardiovascular lesion—these two giving a total of 58% of the whole. Of the rest 22% were cripples from rheumatoid arthritis, ununited fractures, &c., 11% included psychiatric cases, lesions of C.N.S., neoplasms, &c., while 9% were inmates for social reasons.

### Cerebrovascular Accidents at Age 65 or Over

The eyes of all this group were examined under a mydriatic, and I want to report specially on the 117 cases that had a cerebrovascular accident.

The Eye Condition of 117 Cases with a Cerebrovascular Accident of Age 65 and Over

| | Age 65/74 (43 cases) | Age 75/84 (63 cases) | Age 85 and over (11 cases) |
|---|---|---|---|
| Normal .. .. | 16 | 16 | 3 |
| Sclerosis retinal vessels | 15 | 23 | 3 |
| Retinopathy .. .. | 9 | 14 | 2 |
| Opacities of mediæ .. | 3 | 8 | 3 |
| Glaucoma .. .. | 0 | 2 | 0 |

Note: Sclerosis of retinal vessels may be slight to extreme but there is no retinopathy. Retinopathy (including optic atrophy) nearly always discrete degenerative type, rarely hæmorrhages or exudates. Opacities of mediæ nearly always lenticular—rarely corneal or vitreous.

It was especially interesting to find so relatively little opacification of the mediæ, and this made examination of the fundi an easy task. One could assess how the function of retinal irrigation was being carried on, and also the state of the retinal vessels.

### High Blood Pressure

High blood pressure has almost no known cause. It is well known that there are a group of individuals who constitutionally and genetically are predisposed to develop blood pressure well above the average with increasing age. There is, however, no arbitrary means of separating hypertensive individuals from normotensive ones.

A blood pressure of 155/90 may be taken as the highest normal figure, but with advancing years and less recoil in the great vessels the systolic pressure may be expected to rise. It is the diastolic pressure, however, which is all-important—it represents the resistance which ventricular contraction must overcome to open aortic valves and approximates more closely to the mean blood pressure. The prognosis in hypertension seemingly depends mainly on diastolic pressure. A diastolic above the critical level of say 140 mm. carries a grave prognosis.

Leathem states that a high diastolic pressure gives cardiac enlargement and retinal changes in 89% of cases, while a high systolic with normal diastolic gives retinal changes in only 50% of cases.

In examining the retinal vessels for evidence of vascular sclerosis the changes one regards as peculiar to this state are:

(1) Irregular lumen.
(2) Arteries narrower than veins.
(3) Opacification of arterial wall at arteriovenous crossings causing "nipping" of vein.
(4) Pallor of arteriolar blood column or broad or exaggerated reflexes from the vessels.

Blood Pressure in mm. of Hg of 117 Cases with a Cerebrovascular Accident of Age 65 and Over

| Age | Systolic | | | Diastolic | |
|---|---|---|---|---|---|
| | Highest | Lowest | | Highest | Lowest |
| 65/74 (43 cases) | 240 | 110 | | 120 | 60 |
| | Average: | Systolic | 176 | | |
| | | Diastolic | 97 | | |
| 75/84 (63 cases) | 240 | 110 | | 130 | 70 |
| | Average: | Systolic | 193 | | |
| | | Diastolic | 98 | | |
| 85 and over (11 cases) | 210 | 140 | | 120 | 70 |
| | Average: | Systolic | 165 | | |
| | | Diastolic | 93 | | |

Of the 117 cases under review 43 were in the first age group, 65–74. About one-third of these cases showed normal fundi, while a further one-third had definite vascular sclerosis but no retinopathy. The estimation of vision in these cases is difficult as many are bedridden, mentally confused, &c., but about 50% of "no retinopathy" cases took quite an interest and were able to read.

The other two groups (75–84 and 85 and over) showed a somewhat similar state of the fundi, but the general cerebral condition was definitely worse in the oldest age group. The review of the blood pressure in this series of cases is interesting. The relatively good condition of the fundi is in keeping with the low average diastolic pressures in all these groups—actually only 2 cases had a figure over 120. On the systolic side an average of 180 for these age groups is also on the low side. Perhaps the sheltered life and good care they receive has some effect on these figures. However, on the basis of these figures one might add to Leathem's statement about retinal changes with high diastolic and systolic pressures, and say that with reasonably normal diastolic and systolic pressure in these older age groups only 25% show any retinopathy. Admittedly another 35% showed evidence of retinal vascular sclerosis. Lyle points out that these arteriosclerotic vascular diseases usually occur above the age of 60 and the retinopathy, if present, is of a dry, hard or discrete type. On the other hand the hypertensive arteriolopathy occurs in the 40–60 period and is associated with hæmorrhages, œdema and soft exudates.

The discrete use of the hypertensive drugs, anticoagulants, sedatives, diet, &c., will no doubt bring these two groups closer together, but it would seem that the basic underlying aetiology is different. Possibly very few of the hypertensive arteriolopathy group reach the age of 65, and this would seem to be confirmed by my geriatric survey.

### The Healthy Aged Person in an Old People's Home

To turn from the frail and infirm old people to a group of persons who begin their lives in an old people's home in a relatively fit condition:

Clifton House was founded over one hundred years ago and is run by the Belfast Charitable Society. The persons admitted must be 65 years of age or over and must pass a cursory medical examination as to their relative fitness. Social considerations are the main criteria for admission, but no persons are admitted who are likely to become a nursing liability in the immediate future. Once admitted, however, they are kept until they die. Three inmates are centenarians, the oldest being a man aged 104 who can still read small print and is mentally and physically fit. He goes for a one mile walk into the city centre daily. A second man, at the age of 102, can still see to get around and look after himself, but the third member (a woman) has very poor sight.

Old People's Home

| | Age 65/74 | Age 75/84 | Age 85 and over |
|---|---|---|---|
| No. of cases .. .. | 15 | 81 | 42 |
| Can read with glasses .. | 14 | 74 | 36 |
| Cause of defective vision | 1 glaucoma (also senile) | 1 fundus degeneration<br>6 lens opacities<br>6 senile but 3 can read | 1 fundus degeneration<br>5 lens opacities<br>9 senile but 7 can read |

(Senile means senile mental degenerative changes.)

The overall picture of the 138 persons in the home shows that no less than 90% can still read with glasses. Of the 14 cases who are unable to read there was 1 case of glaucoma, 2 with clear mediæ but obvious arteriosclerotic fundus defects, while the remainder are due to varying degrees of lens opacities. Only 3 cases of cataract have had an operation but more than 50%, while unable to read, are able to get about, feed themselves, &c.

Of 16 cases (12%) with obvious senile mental degenerative changes like confusion, disorientation, &c., no less than 10 can still read and have no gross eye lesion. Thus it would appear that in these well-cared-for old folk the structures of the eye were withstanding the ageing process as well as, or even better than, the general cerebral structures—only 14 persons are unable to read, while 16 have obvious mental degenerative changes.

### Conclusion

We have been privileged to live in an age when much has been accomplished to preserve vision. Active trachoma to-day is almost non-existent in this country, and most of the acute and subacute infective lesions have their antidotes—a truly wonderful advancement for our generation.

Looking at the inmates of the Old People's Home one can see that it is not necessarily the number of years that counts, but rather the state of the tissues. Therefore it would seem that one of the most important things to do is to choose one's ancestors correctly!

Surgery can remove a cataract successfully and perhaps stabilize glaucoma, but prevention will always be better than cure.

Living in this fast-moving age of change the fundamental ophthalmological research unit must be linked on the one side with general medical research, and on the other with local clinical research. It is probably to the former that we may look for major advances, but each one of us in his own sphere must try to make some contribution, however small, to the many unsolved problems, and so alleviate that "Last scene of all, That ends this strange eventful history", that it may not be "Sans teeth, sans eyes, sans taste, sans everything".

### REFERENCES


Gunn, M. (1898) *Trans. ophthal. Soc. U.K.*, **18**, 356.

Leathem, A. (1949) *Quart. J. Med.*, **18**, 203.

Linn, L., Kahn, R. L., Coles, R., Cohen, J., Marshall, D., and Weinstein, E. A. (1953) *Amer. J. Psychiat.*, **110**, 281.

Lyle, D. J. (1945) Neuro-ophthalmology. Springfield; p. 264.

Platt, R. (1947) *Quart. J. Med.*, **16**, 111.

—— (1956) *Trans. ophthal. Soc. U.K.*, **76**, 501.

Registrar-General (1955) Statistical Review of England and Wales. London.

Sorsby, A. (1956) Blindness in England, 1951–54. Ministry of Health, London.

Walsh, F. B. (1947) Clinical Neuro-ophthalmology. Baltimore; p. 318.

Walton, H. (1854) *Med. Times Gaz.*, n.s. **9**, 266.

Wheeler, J. R. (1953) *Trans. ophthal. Soc. U.K.*, **73**, 550.

# Section of Endocrinology

President—C. N. ARMSTRONG, M.D., F.R.C.P.

[*October* 23, 1957]

## The Clinical Diagnosis of Sex

PRESIDENT'S ADDRESS

By C. N. ARMSTRONG, M.D., F.R.C.P.

I HAVE chosen the problem of sex for this Address because of present-day interest in the subject, and I propose to make a clinical approach to the problem.

### CLINICAL PROBLEMS OF SEX

The *physical abnormalities* seen often concern the external genitalia, but other situations arise. Most frequently the sex decided at birth becomes questioned when supposed hypospadias requires repair; signs of precocious puberty appear; a young girl develops male pattern hair or primary amenorrhœa; or a young male has testicles which fail to descend, possibly together with signs of deficiency of secondary male characteristics. Occasionally the surgeon questions the true sex fortuitously at operation. For example, a colleague operated for acute appendicitis on an 11-year-old girl who was found to have no uterus due to the presence of the Testicular Feminization syndrome. Lastly the true state may emerge from the exercise of "sixth sense". An elderly "woman" was admitted to the general ward of a hospital from an old people's home, and one of the patients objected on the grounds that she thought that the patient was a man. This patient turned out to be a case of true hermaphroditism.

The psychological problems fall mainly within two groups. *Transvestism* or *Eonism* can be present in a male who may have more or less pronounced male physical characters, and the opposite situation may arise in the female. *Homosexuality* includes individuals whose emotional libido is directed to another person of the same sex. The behaviour may be active or passive, or both active and passive.

It is in these forms that various clinical problems have reached me. The correct sex diagnosis in itself may be important to the patient for determining the pathology and treatment in appropriate instances, or for legal reasons associated with inheritance or athletic competition.

### THE CRITERIA OF SEX

Certain criteria may be applied in establishing the final diagnosis which I would say are: (1) Nuclear sex pattern; (2) gonadal status; (3) chemical evidence; (4) external anatomy; (5) psychological sex.

### NUCLEAR SEX

Normally, an X or Y spermatozoon fertilizes an X ovum. The female factor X is represented by 1 and there are 1½ male factors carried in the autosomes; the Y is blank. Thus XX amounts to 2 female factors against 1½ male—this gives a predominance of 2 : 1½ in favour of female and the result is female. X Y amounts to 1 female against 1½ male and the result is male. The basic sex is female, the male being a further development from this. Sometimes the genetic factors may not be constant; for example it has been suggested by Sachs that there are women who are XXX and there may be individuals, both male and female, who carry in the autosomes a higher value of male factors than is represented by 1½. It is not known by what means the undifferentiated gonad in the fœtus at 7 weeks is influenced to develop into a testis with the development of subsequent male characteristics. XX causes the cortical part of the gonad to be differentiated and the XY the medullary part. It is highly probable that genetic factors determine the sensitivity of tissues to hormones, abnormality of such sensitivity causing some types of intersex. Barr noted in nervous tissue an intranuclear satellite body only present in the female. In other tissues 30% to 70% of the cells of females were found to have a small body adjacent to the nuclear membrane compared with only 5% of a similar structure in males. Later Davidson and Smith found a projection or "club" in about 6 out of 500 polymorph nuclei from females and none in those from males. This work is important in the problem of intersexes since those individuals with chromatin positive cells would, if the theory that Barr's bodies are hetero-chromatin derived from two X chromosome is correct, seemingly have XX chromosomes. The presence of this body would thus indicate the genetic sex of the individual whatever might have been the ultimate somatic or psychological development.

*Gonadal status* was at one time naturally thought to be the most important. The gonads might seem to determine the correct sex of the individual, and in the past I think that they would have been accepted for the legal definition. Since the detection of the nuclear sex pattern in the various syndromes it can no longer be said that the gonad is the all-important factor.

*Chemical evidence.*—There is no doubt that hormones play a very large part in the

| | Normal female | Simple constitutional masculinism | Adreno-genital masculinism | Female homosexual | Female transvestism | Female intersex I without adrenal disorder | True hermaph-roditism | Turner's syndrome | Swyer's syndrome | Male intersex II "testicular feminisation syndrome" | Klinefelter's syndrome | Male transvestism | Male homosexual | Adreno-genital feminism | Simple constitutional feminism | Male with hypospadias | Normal male |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NUCLEAR SEX CHROMATIN | + | + but lesser % in polymorphs | + | + occasionally in polymorphs | + | + | + or − | − rarely + | − | − | + rarely − | − rarely + | − | − | − | − | − |
| GONADS | ○ ○ | ○ ○ | ○ ○ | ○ ○ | ○ ○ | ○ ○ | ○ ● | | ? | ● ● | • • | • • or normal | ● ● | ● ● | ● ● | ● ● | ● ● |
| HORMONES: OESTROGENS | normal F. | | | normal F. | normal F. | normal F. | | | high | normal M. | not increased | n. to >n. for male | normal M. | probably >n. for male | | normal M. | normal M. |
| HORMONES: ANDROGENS | normal F. | increased for female | increased for female+++ | normal F. | normal F. | normal F. | normal or low | low | normal | normal M. | < normal | deficient for male | normal M. | increased++ | diminished for male | normal M. | normal M. |
| EXTERNAL ANATOMY |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PHALLUS: PENIS | | | | | | | normal penis − or enlarged clitoris | | | | small to moderate size | small | normal size | normal size | small | small (often mistaken for enlarged clitoris) | normal size |
| PHALLUS: CLITORIS | normal size | normal size | enlarged | normal to enlarged | normal to enlarged | enlarged++ | | normal size | normal to enlarged | normal size | | | | | | | |
| MICTURITION | ♀ | ♀ | ♀ | ♀ | ♀ | ♀ | ♀ | ♀ | ♀ | ♀ | ♂ | ♂ | ♂ | ♂ | ♂ | ♀ | ♂ |
| MENSTRUATION | normal | irregular or amenorrhoea | absent | normal or irregular | normal or irregular | normal | usually absent | absent | amenorrhoea | absent | | | | | | | |
| FERTILITY | + | + or − | − | + | + | − | − | − | − | − | − | − or + | + | − | + | − | + |
| PSYCHOLOGICAL SEX | F. | F. | F. | M. or F. | Neutral or M. | F. or M. | F. or M. | F. | F. | F. | Neutral or M. | Neutral or F. | M, F. or both | M. | M. or rarely F. | M. | M. |
| AETIOLOGY | genetic | genetic±/or hormone | genetic±/or hormone | genetic or psychological | genetic | genetic | genetic | genetic | genetic | genetic | genetic | genetic | genetic or psychological | hormone | genetic±/or hormone | genetic | genetic |

physical development and other features of the individual and their estimation is valuable in certain syndromes, for example the adreno-genital syndrome, and gonadal dysgenesis. I doubt whether it is possible at the present time to say, on purely chemical grounds, what might be the sex of an individual.

*External physical characteristics* are important in influencing our minds on the nature of an individual's sexual status.

*Psychological sex* is of particular importance when it is different from the main physical characteristics indicative of external anatomical sex. Transvestism is also named Eonism after the Chevalier d'Eon de Beaumont, who was a diplomatic agent of Louis XV, and was taken to be a woman, but proved at post-mortem to be a normal man. Transvestism is an inaccurate term for the description of such cases, for the preference to wear feminine dress is only one expression of a strong desire to become identified with women, and to be regarded as a female by society. Other characteristics of eonism are the fantasies of pregnancy, passionate longing for a maternal role, preference for feminine games and activities, and a desire for castration in an attempt to achieve anatomical resemblance to a woman. This preference for the feminine role is evident from early childhood.

The condition is relatively common, but second in frequency to homosexuality. It may be symptomatic of homosexuality or other perversions, but only a small proportion of homosexuals are transvestites. The conditions are probably quite distinct for these reasons: the crucial desire of the homosexual is for sexual relationship with a person of his own sex whereas the eonist is repelled by the physical aspects of such relations and responds with disgust and revulsion. If an active sexual life is led by an eonist it is more often an heterosexual one, as in the case of Chevalier d'Eon and Abbé de Choisy. The evidence for regarding transvestism as being of a constitutional nature, doubtless on a genetic basis, perhaps can be even more readily accepted than in the case of homosexuality, because it is a phenomenon manifested so early in life and, in most instances, there are striking feminine characteristics of physique. There is no sound evidence for accepting the contention of psychiatrists that it is due to a castration complex or other environmental psychological factors, e.g. female dominance in the home.

*Homosexuality*.—By contrast homosexuals as a rule do not want to change their sex, and identity. I am surprised that even recently published works on endocrinology (e.g. Wilkins) still make the statement that the psychological sex is that according to which the individual has been brought up; if this were so man would be the only animal dependent on his environment both for his sexual libido and for the survival of the race. Surely this is fantastic! To quote Broster, the sexual act is so instinctive that it has not even to be learned but must be of genetic origin. All my cases of boys and men with hypospadias, brought up as "girls" have a male psychological outlook. The present attitude to homosexuality is similar to the attitude in the past to physical and mental illness, although I think scientific opinion is coming round to the view that the condition can be one of genetic and not environmental determination.

## Spectrum of Sex

Fig. 1 has been drawn for me by Mr. D. P. Hammersley mainly from photographs of my own cases. It gives his impression of the stances and features of cases of intersex. Beginning at the red end of the spectrum on the left is a normal woman, which is the basic sex, passing to the deviations from the normal, through the intersexes, to the blue end of the spectrum, the normal man. Various intersexes may occur, mostly as a result of purely genetic factors and of hormone influence, itself of genetic origin or acquired, or of failure of the target organ to respond to hormones. Fig. 1 is not intended to be scientifically correct in all details; it does not include all the syndromes, nor have I grouped, for instance, cases of gonadal dysgenesis together. It represents the way the problem of gradation of sex, including psychological sex, impresses me. I have taken permissible licence in a Presidential Address: I know I shall be criticized for including disorders of psychological sex amongst the physical intersexes, but in my opinion it is where they should be and where they will eventually arrive.

## The Clinical Diagnosis of Sex and Management

I should like, after the above remarks, to return to the clinical problems. Firstly *the patient with female micturition and large phallus*. Is this individual, in whom often hypospadias is diagnosed, in fact a boy or a girl? The patient will be a boy if the nuclear sex is male, and external male characteristics are present with the exception of the hypospadias; testes may be present or undescended. He should be regarded as of male sex and the hypospadias repaired. The patient will be a girl if the nuclear sex is female, and female external characteristics and ovaries are present. This may not be evident before puberty, particularly in that type of female intersex without endocrine disorder. It is important in such cases to estimate the urinary 17-ketosteroids. If the ketosteroids are normal and the patient has a uterus and ovaries, and is young, I would advise plastic

surgery if required and the adoption, if necessary, of female sex. If the ketosteroids are unduly high the presence of the adreno-genital syndrome would be indicated; in such cases treatment with cortisone should be begun early so that the normal development of female characteristics can occur. The *patient with female characteristics and primary amenorrhœa with or without pubic hair and normal or slightly enlarged clitoris* may manifest the Testicular Feminization syndrome, Turner's syndrome or Swyer's syndrome. "She" may have male nuclear sex and retained testes, which abnormalities may be considered of academic rather than clinical interest. The fact that pubic hair is absent in the Testicular Feminization syndrome and not made to grow by testosterone suggests that the cause of the Syndrome is lack of response of the target organ to the male hormones for genetic reasons. In my opinion patients of all these types should continue as females but they could raise a difficult legal problem, particularly if inheritance or athletics were involved. Until this question is fought out in the court we do not know the legal position. *Cases of poorly developed male characteristics, poor masculine hair, small penis, small testes, and with or without gynæcomastia.* Like the last group they may be found to have nuclear sex opposite to the external anatomy. In Klinefelter's syndrome the nuclear sex is usually female, suggesting they are masculinized genetic females. Yet in fact the external anatomy is male, and spermatogenesis does rarely occur, so it is better to regard them socially as males. The only legal complication which may arise if they are regarded as males would concern such an individual who is also a transvestite or homosexual. Such patients have been put in prison for following their psychological sex libido, even when the nuclear sex is female. Again thus far all the facts have not been presented in court. Under this general heading there are also patients simply having poor masculine development of genetic origin or due to hormonal deficiency, and those boys with adipose gynandrism (Simpson). *Patients with psychological sex abnormalities* immediately raise immense problems. No one surely will contend, after scanning the whole spectrum of sex with all its physical inconsistencies, that it would be reasonable to assume that the psychological sex must correspond to the other sexual criteria. Prejudice is so deeply embedded that I doubt if we have reached a stage when the general public, or even the medical profession, would accept that psychological sex may differ from physical sex and can be of genetic rather than of environmental origin. If this view is accepted society can hardly be held responsible. I am prompted to ask, which is the more important, the body or the mind? The law of Great Britain, so far, is definite on this: it is the body. The law has no sympathy with the individual who has female psychological sex in a male body, nor has the general public. Without a physical background, it would be too much to expect the law to define sex merely upon psychological grounds. Although it may come to be accepted that there are individuals who are genetically psychologically of one and physically of the opposite sex and should be allowed to follow a life in accordance with their psychological sex, the registered sex of these individuals must, I would say, remain as determined by their physical characteristics.

## Conclusions

To sum up, my advice in intersex would be:

In cases of female micturition with large clitoris, always determine the sex by modern methods of nuclear sexing, ketosteroid excretion, &c., and advise that such cases be brought up as their correct sex. If they have been brought up in the wrong sex, carry out the necessary treatment, plastic, hormonal or both and advise that they change to their correct sex, even in adult life.

Those cases of intersex whose nuclear sex or gonads are not consistent with the external sex anatomy should be told nothing, but allowed to continue with the sex already assumed by their external body form which should be enhanced with treatment if possible. I would advise that the legal sex be that of the individual's external anatomical sex.

Where the psychological sex is opposite to that of the body, I think it is the duty of society to allow those individuals to live as their true sex emotion directs, provided it does not interfere with the welfare of other persons, but the legal registered sex should be that of the external anatomy.

In the case of transvestites, I should support the proposal of Dr. Peter Bishop, that a small committee should be set up to investigate such cases and have the legal right to advise any plastic surgery they consider necessary.

I shall conclude by quoting from Milton's "Paradise Lost."

> "For spirits when they please
> Can either sex assume, or both, so soft
> And uncompounded is their essence pure."

I wish to thank for their help Professor Martin Roth, Professor of Psychological Medicine, Dr. J. E. Gray, Lecturer in Anatomy, Mr. C. J. Duncan, Director of the Department of Photography, and Mr. D. P. Hammersley, Medical Artist, in the University of Durham.

REFERENCES.—Barr, M. L., and Bertram, E. G. (1949) *Nature, Lond.*, **163,** 676. Broster, L. R. (1944) Endocrine Man. London. Davidson, W. M., and Smith, D. R. (1954) *Brit. med. J.*, ii, 6. Klinefelter, H. F., Reifenstein, E. C., and Albright, F. (1942) *J. clin. Endocrinol.*, **2,** 615. Damon, M., and Sachs, L. (1957) *Lancet*, ii, 20. Simpson, S. L. (1948) Major Endocrine Disorders. 2nd Edn., p. 63. London. Swyer, G. I. M. (1955) *Brit. med. J.*, ii, 709. Turner, H. H. (1938) *Endocrinology*, **23,** 566. Wilkins, L. (1957) The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. 2nd Edn., p. 287. Oxford.

# Section of the History of Medicine

President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., C.B., M.A., D.M., F.R.C.P.

[*October* 2, 1957]

## Julius Cæsar and the Falling Sickness

By TERENCE CAWTHORNE, F.R.C.S.

THE idea for this paper came when I was re-reading Shakespeare's "Julius Cæsar" at a time when I was preparing an article on Ménière's disease. In the very same Scene, and separated by but a few lines, the following statements are made:

JULIUS CÆSAR (*who has been talking to Antony about Cassius, ends by saying*):

"Come on my right hand, for this ear is deaf."

Then shortly after, in a discussion about Cæsar between Cassius, Casca and Brutus, the latter says:

"'Tis very like he hath the falling sickness."

Now it has always been assumed that Julius Cæsar suffered from epilepsy, but unilateral deafness and the "falling sickness", I thought, could mean Ménière's disease, and so I have been enquiring into the life and times of Julius Cæsar, with particular reference to his falling sickness.

As the 2,000th anniversary of his death by assassination fell on March 15, 1957, it seems an appropriate time to discuss his disorder and to recall his remarkable career which was brought to a brutal end by a determined band of his associates, many of whom he regarded as trusted friends. Though he was the most powerful and the most popular man in the civilized world, and though it was freely admitted that he had done more for the glory of Rome than any other citizen, he had by his remarkable and versatile talents shown up the lack of ability in many others; earning the envy and malice of those around him whose ambitions were so much greater than their often meagre abilities.

A Patrician by birth, his was one of the oldest and noblest Roman families, the Julians, and when his aunt Julia, who had married the Democratic or Popular dictator Marius, died, he said in the funeral oration:

> "On her mother's side Julia descended from the ancient Kings, on her father's from the Immortal Gods Themselves. Her mother and my grandmother, Marcia, descended from Marcius, the fourth King of Rome: while we of the Julian House trace back our origin to Venus Herself. In our family, therefore, we combine the Divine Right of Kings, who are the greatest among men, and the Worship of the Gods, to Whose Power even Kings must bow."

Though obviously proud of his family and possibly not unmindful of his destiny, he was no idle boaster when it came to his own deeds as set out in his "War Commentaries". It could never be said, however, that he hid his light under a bushel; indeed, it would have been difficult so to do as his great deeds shone out.

In view of his noble origin, it might be thought that Julius Cæsar would follow the Optimates or Republican Party, which included nearly all the Patricians. Instead he joined their opponents, the Populares or Democratic Party to which the middle classes

gave allegiance. In this, no doubt, he was influenced by his uncle, Marius, who had been the leader of the Populares. After the eclipse of Marius when Julius Cæsar was a youth, Sulla the champion of the Optimates came to power and dealt very severely with his political opponents. Fortunately for the Roman Empire, the youth Julius was left alone, though he had to travel abroad for some time.

Despite the great care taken to avoid any individual form of dictatorship in the Roman State, it gradually came about that political power was concentrated into the hands of a comparatively small group of Patrician families who saw to it that they dominated the Senate. Consequently many of the Laws which were passed favoured the Patrician and land-owning classes. Successful wars brought more slaves into Roman hands, and these slaves went to swell the estates of the landowners who were able to cultivate their land with cheap slave labour. The smaller farmers could not compete and sold their farms to seek their fortune in the capital, thus adding to the number of the "hangers on" and unemployed. Successive political leaders vied with one another to gain popularity, and the increasing inefficiency and corruption of both Parties were undermining the State, so that the time was ripe for a man with that rare combination of ambition and ability to rescue the Roman Republic from the slough of corruption and selfishness which was threatening to engulf it. Though we know that Julius Cæsar was the man to do this it took him fifty years of pushing, bribing, intriguing and fighting to convince his contemporaries of this. And even when he had succeeded, they could not forgive him and despite all he had done for them and for the State they murdered him; though they preferred to call it "tyrannicide".

This was a political blunder, for Cæsar was the one man who could have built upon the old foundation a solid and workable government. His assassination involved the State in fresh struggles and civil wars, until in the end it fell under the supremacy of Cæsar's heir and nephew, Augustus, who established a far more despotic rule than that which the so-called liberators had attempted to avert.

Born in the year 102 B.C., Cæsar was, thanks to his uncle Marius' influence, given, of all things, a senior religious appointment as Flamen Dialis at the age of 15. This gave him a seat in the Senate but precluded him from taking an active part in war or politics. This did not last very long and at 19 he went abroad, gaining experience in war as an aide-de-camp and as an orator and lawyer from the leading teachers in the Grecian Islands. This included an episode at the Court of King Nicodemus which later on was magnified by his opponents into a homosexual scandal. However, his conduct in more mature years shows that if this incident ever occurred it was but an adolescent prank, for Sir Charles Oman refers to him later as "the inevitable co-respondent in every fashionable divorce". Returning to public life in Rome at the age of 30 he achieved the coveted Consulship by the age of 42.

He was not too particular about the means he employed to reach this post which has been described as a "carnival of illegality and mob law, which made a fitting close to the whole of his demagogic career".

Once his Consulship was over he took over the pro-Consulship of the Gallic Provinces, at the same time forming an uneasy alliance with the financier Crassus and the ex-soldier Pompey. This was known as the Triumvirate and each was of equal Consular rank and power. Cæsar left for his Gallic Province and it was ten years before he returned to Rome, having in the meantime conquered the whole of Gaul, contained the Germanic hordes and invaded Britain twice.

Despite his previously slight military experience Julius Cæsar soon proved to be an exceptional leader in war. He was not only a great strategist and military tactician but he was also a leader of men. Many were the times that he, personally, led his men into battle, and he was often in the thickest of the fight. As an orator and as a politician he was unequalled and by sheer force of intellect he could persuade men to his way of thinking, equally well in committee, in the political arena or before a group of tired and even rebellious soldiers. Even the eloquent though vacillating Cicero, the silver-tongued orator, was compelled to admit that he had met his master in Julius Cæsar; but he never forgave Cæsar for this, and I believe that it was he, Cicero, who was behind the plot to kill Cæsar.

At the end of the Gallic campaign Cæsar fought his way back to Rome from which his opponents, the Senate (headed by Pompey) had fled, but four more years of fighting in Spain, Greece, Africa and again Spain were needed before he finally returned triumphantly to Rome.

During the year that was left to him he laid the foundation of a new autocracy headed by a Sovereign to rule the Roman Empire in the place of the Senate and the people. His

names have been immortalized in the month of July and in the title of Cæsar, Czar and Kaiser. He forgave his political enemies; but this was his undoing, for they could not forgive him.

As a young man he was undersized and delicate, but he grew up to be virile, tough and even licentious. Though he loved luxury and power, he never over-indulged in eating or drinking, and between the ages of 40 and 55 lived the hard life of a soldier on campaign. Always in the public eye, any disorder, infirmity or even slight accident is sure to have been noted and even magnified. We have heard of his baldness and of his amours, and even when he stumbled and fell when disembarking on to African soil during the Civil War this was noted by Plutarch. I am sure that if he had been subject to real epileptic fits we would have heard much more about them than has come down to us from the writers of those times.

Our main source of information about Cæsar's "falling sickness" comes from "Plutarch's Lives" in which it is mentioned three times.

The first was part of a general description of Cæsar—

> "he was lean, white and soft-skinned, and often subject to headache, and other while to the *falling sickness*, the which took him the first time, as is reported, in Cordoba."

Now Cæsar was three times in Spain. The first time was before he was Consul, the second in the early stages of the Civil War before he defeated Pompey at Pharsalus, and finally after the African campaign when he was dealing with Pompey's son and his followers. This must refer to the second campaign in Spain as Plutarch's next reference to the sickness is in the African campaign at the battle of Thapsacus against King Juba and Scipio. When he did not take his usual place in the forefront of the battle Plutarch says:

> "For as he did set his men in battle the falling sickness took him, whereunto he was given, and therefore feeling it coming, before he was overcome withal, he was carried into a castle not far from thence where the battle was fought, and there took his rest till the extremity of his disease had left him."

Plutarch's third reference is to the time when the populace offered Cæsar the Emperor's crown and he refused it three times:

> "Notwithstanding it is reported that afterwards, to excuse this folly, he imputed it to his disease, saying that their wits are not perfect which have this disease of the *falling evil* when standing on their feet they speak to the common people, but are soon troubled with a trembling of their body and a sudden dimness and giddiness."

It may be noted that in none of these three statements is there any reference to loss of consciousness, to foaming at the mouth, to twitching of the face or limbs, or indeed to any of the other manifestations of epilepsy.

Plutarch, the Greek philosopher and biographer, was born in the reign of Claudius, half-way through the first century, A.D. He wrote in Greek and his most famous work, his "Lives," compares and contrasts the Greek and Roman heroes. His is the most contemporary and the fullest life of Cæsar.

There is another by Suetonius, the first in his series of "The Lives of the Cæsars." This was written some seventy years after Plutarch. Suetonius had the advantage of being Secretary to the Emperor Hadrian and in this position had access to Imperial Archives. His "Life of Cæsar", written in Latin, makes but one short reference to Julius Cæsar's ailment—"He was twice attacked by the *falling sickness* during his campaigns".

As might be expected Cæsar himself makes no reference to this sickness in any of his works, nor is it mentioned by Cicero, Lucan or Dio Cassius.

Shakespeare's source of information about Julius Cæsar came from Sir Thomas North's translation of "Plutarch's Lives"; and it was Sir Thomas North who coined the term "*the falling sickness*". He did not translate direct from the Greek, but from the French of James Amyot, Bishop of Auxerre. There is no mention in Plutarch, or in any other Greek or Roman author, of Cæsar being deaf, even in one ear.

The only reference I can find to Julius Cæsar's deafness comes from George Wherry in "Notes and Queries" (1909), Series 10, Vol. XL, p. 243.

> "*Julius Cæsar's Deafness*—Shakespeare makes Julius Cæsar deaf in the left ear. To Mark Antony Cæsar says: 'Come on my right hand, for this ear is deaf'; and his attacks of epilepsy are also noted in the play—'He hath the *falling sickness*'. It is quite possible that attacks of giddiness associated with Ménière's Disease of the ear may have been mistaken for epilepsy. The Romans were familiar enough with

epilepsy, which they called 'morbus comitialis', from the attacks witnessed in the Forum or Senate House which broke up the Assembly; and it is unlikely that aural vertigo was understood at that time."

Where, then, did Shakespeare get his reference to Julius Cæsar being deaf in the left ear? It has been suggested that there might be some political significance in this, but it cannot be in the modern sense, for the term "Left Wing" and "Right Wing" only became significant in the Assembly of the French Revolution. Again, could it be that Cæsar was suggesting that he was going to forget what had just been said? But as he had just been doing all the talking and very little listening, there is little point in this suggestion. As there does not appear to be any mention of Cæsar being deaf in any of the references available to Shakespeare he may have put this in so as to add a touch of realism to the part. We know that Shakespeare always made his great historical figures behave like ordinary human beings; and indeed it is just that homely touch which makes his characters live. It could well be that Shakespeare knew someone or possibly more than one person who was troubled with the "falling sickness" and deafness, and that he introduced the deafness in one ear in order to make Cæsar like other men. There is no reason to suppose that the deafness was brought in to help the stage business.

But even if we are to deny Cæsar's deafness on the grounds that we have only Shakespeare's word for it, we are still left with his "falling sickness". Plutarch, writing in Greek, refers to this as "Epileptikois", a term used in those days for any seizure that caused the sufferer to fall down and be helpless. It is not surprising that many writers translated this as epilepsy, and so the term "falling sickness" and epilepsy have been loosely regarded as the same thing. Suetonius, writing in Latin, uses the term "morbus comitialis", the disease which, when it attacked a member of a committee, ended the meeting. Clearly such a description could include epilepsy, a stroke, a heart attack and also an attack of Ménière's disease.

Now, as Cæsar's mental and physical powers remained unimpaired between attacks, it seems unlikely that they were caused by heart disease or a cerebral catastrophe. This leaves epilepsy and Ménière's disease.

When the "falling sickness" first overcame him, Cæsar was in the early fifties, a common time for Ménière's disease to start. As the most famous man of the Ancient World, there was no shortage of writers and poets to publicize his failings as well as his strength. Had he really suffered from epilepsy it is difficult to believe that it would have been passed over in the few words that have come down to us. Nor can it be said that the Romans were unacquainted with epilepsy, for here is a description given by Lucretius of an epileptic fit:

"Oft times with violent fits a patient falls,
As if with thunder struck; and foams and bawls,
Talks madly, shakes, moves here and there, breathes short,
Extends and tires his limbs with antic sport;
. . . . . .
His weakness wears and he forgets his pain;
His strength, his life, his sense return again."

Had Cæsar suffered from major epileptic seizures, surely these sensational attacks would not have been passed over so lightly by the careful biographer Plutarch, or by the gossip Suetonius.

Had these attacks been something more serious than a labyrinthine disturbance, they must have left a greater mark on the man who, for the last fifteen years of his life, extended and dominated the Roman State. A man, moreover, who could at the end of twelve years' continuous fighting and political intrigue take time off to share with Cleopatra one of the great love affairs of the world.

That it could have been a minor form of epilepsy cannot be denied, though sufferers from *petit mal* so often are troubled also with bad tempers, fits of depression, or some form of neurosis and there is nothing to suggest that Cæsar was ever affected in any of these ways. Coming on at that time of life and not leading to any deterioration of mental or physical powers it is, in the light of our present knowledge, much more likely to have been a benign disorder such as Ménière's disease.

We are still left with the problem of deafness, and though I have been unable to trace any contemporary account of Cæsar being deaf, I shall always be grateful to the memory of Shakespeare—not only for the plays which we enjoy, but for suggesting an alternative and, to me, plausible cause for Cæsar's "falling sickness".

# Section of Surgery

President—A. DICKSON WRIGHT, M.S., F.R.C.S.

[*October* 2, 1957]

## DISCUSSION ON HIATUS HERNIA

**Mr. Norman C. Tanner** (London):

Hiatus hernia is a deformity which may exist through life without producing any notable disturbance, or it may give rise to complaints varying from slight breathlessness on exertion to the most severe dysphagia. With large hernias, cardiac and pulmonary symptoms such as palpitations or breathlessness on exertion may be present. At times, the main symptoms may be the result of distortion of the contents of the sac, such as gastric volvulus with transient gastric obstruction. Often the symptoms of a patient with a hiatus hernia are due to another condition, e.g. peptic ulcer, biliary disease, or abdominal carcinoma (Tanner, 1955*a*). The most important effects of hiatus hernia, however, result from reflux of gastric juice, leading to congestion or even deep ulceration of the gullet. The symptoms are heartburn, pain, anæmia and, when cicatrization takes place, dysphagia.

The treatment of hiatus hernia is nearly always medical in the first place. Reduction of the volume of gastric content is aided by taking small frequent meals. Alkalization diminishes the erosive powers of the juice. Reflux is minimized by avoiding recumbency and stooping and by diminishing intra-abdominal tension. Weight reduction and avoidance of belts and corsets significantly lower intra-abdominal tension. Stricture dilatation is occasionally needed in the aged. Surgical repair is indicated as a prophylaxis against œsophagitis in infants and young people. In young adults with large hernias, repair may be required in order to improve respiratory and cardiac efficiency.

The ideal surgical treatment of a hiatus hernia is repair of the hernia before œsophageal damage has occurred. Once deep œsophageal ulceration and fibrosis have taken place, the mechanism of the cardia is so distorted that simple repair is less effective, though some success may follow repair even in these late cases.

*Lines of Treatment*

For the cases complicated by œsophageal ulcer and stricture, a number of lines of treatment are open to the surgeon. A certain cure of œsophagitis is to transect the gullet above the stricture and anastomose it to a Roux loop of jejunum with or without gastrectomy, but this is a severe procedure. A less severe operation is to resect the stricture and part of the upper stomach, and anastomose the œsophagus to the stomach remnant (upper partial gastrectomy) (Tanner, 1955*b*). The gullet is transected just above the stricture, for the gullet here is fibrous and, unlike the normal gullet, even its outer coat will hold sutures well. As much stomach as can be safely removed is resected and the vagus nerves are transected in order to reduce the acidity of the gastric juice, which will now be regurgitated even more freely than before. The post-vagotomy pylorospasm is best overcome by a coincident gastro-jejunostomy to the pyloric antrum. A pyloroplasty or Ramstedt pylorotomy helps, but is less effective than gastro-jejunostomy.

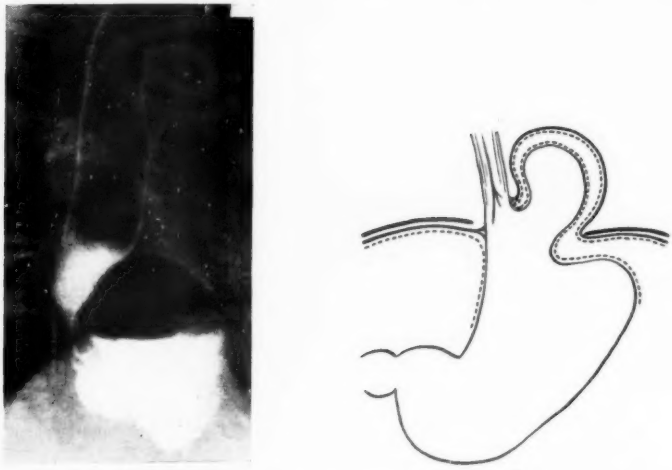
Other operations of still less severity are lower partial gastrectomy, and simple vagotomy combined with gastro-jejunostomy. If lower partial gastrectomy as for duodenal ulcer is done, the stomach stump should be anastomosed to the jejunum rather than to the duodenum owing to the desirability of rapid emptying of the gastric remnant. If a duodenal ulcer is present in addition to the œsophageal stricture, this operation is even more likely to be beneficial. Finally there are various experimental methods such as replacement of the cardia mechanism by an isolated jejunal loop (Merendino and Dillard, 1955), but of which only short-term results are available.

*Operative Technique*

I prefer to approach the hiatus from the abdomen, not only because 20% have an accessory intra-abdominal lesion which is in greater need of treatment than the hernia, but also because the direct view of the crural origins is more convenient for the repair (Tanner, 1955*a*). With good relaxation, aided by excision of the xiphoid process and mobilization of the left lobe of the liver, a good view of the hiatus can be obtained.

In these cases the peritoneal reflections on to the gullet and the phreno-œsophageal ligaments are elongated and thinned, and therefore useless for repair. They are freely

excised until the muscle of the œsophageal hiatus and of the adjacent cardia is laid bare. Only in certain para-œsophageal hernias without reflux is the phreno-œsophageal ligament strong and worth retaining (Fig. 1A, B). The vagus nerves are carefully preserved, since



A B

FIG. 1.—A, X-ray of para-œsophageal hernia without reflux. B, The appearance noted at operation on certain para-œsophageal hernias. The phreno-œsophageal ligament is intact on part of the circumference, but deficient elsewhere, usually to the left side.

otherwise a post-vagotomy pyloric dysfunction will lead to reflux as a result of gastric retention. It is important to dissect the hiatus margins free all round, as otherwise a pad of fat may be left particularly posteriorly, which may be the weak spot initiating a recurrence. Indeed, I believe that the only reason for the improved results when repair posterior to the gullet was instituted, was that the posterior margin of the hiatus was being freed of fat and peritoneal pouches for the first time.

*Types of Repair*

I have repaired the enlarged hiatal opening by several methods. The first was by suturing the margins together in front and behind the gullet by wide interrupted non-absorbable sutures. This method has the disadvantage that some phrenic nerve branches are caught in the sutures at times, and some degree of muscle strangulation may occur. The next method was by imbrication. At operation it can be seen that the muscle fibres to the left of the gullet take origin posterior to the right fibres and so I draw the right margin to overlap the left one, again either anterior or posterior to the gullet (Fig. 2). The third method was by an

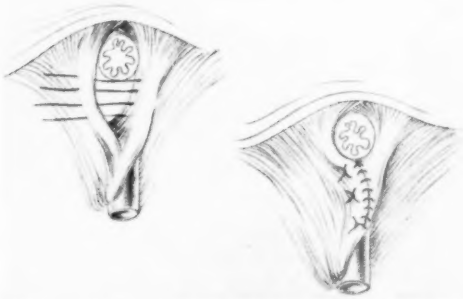


FIG. 2.—"Imbrication" operation posterior to the œsophagus. Note that the fibres of the left margin take origin deeper than that of the right; the overlapping exaggerates this anatomical position.

anterior "darn". If one puts a finger into a normal hiatus, as for example in the operation of vagotomy, the finger is not held by a ring of tissue, but enters a tunnel. About 3 cm. of finger is held posteriorly against the aorta by the fascia spreading from the diaphragm to run down between the anterior margins of the hiatus and the gullet. I believe an anterior repair should be made in an endeavour to reproduce this fascia and exert an even backward pressure on the lower few centimetres of the gullet. The chance of repair will obviously be greater if a canal is formed for the gullet rather than a circular hole (Fig. 3).

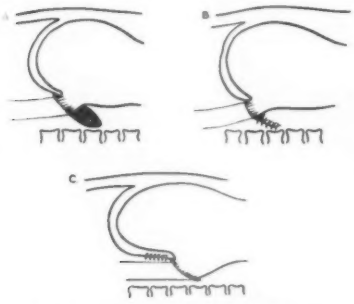



FIG. 3.—Lateral view of hiatus repairs. The posterior repair (B) produces a small hole in a muscle sheet; the anterior repair (C) can be made to produce a tunnel-like passage for the œsophagus.

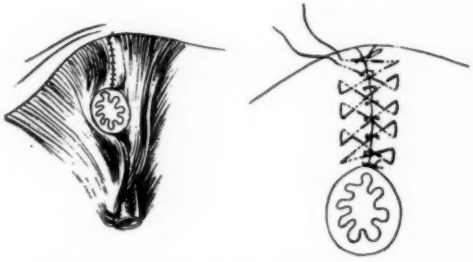


FIG. 4.—Anterior "darn" repair. The edges are sutured together and the sheet of muscle in front of the œsophagus is reinforced with a monofilament nylon darn.

After dissecting the hiatus margins free, I suture the medial edges of the anterior margins together. This gives a thin sheet of longitudinal muscle in the area in which I desire to produce a strong fascia. I now introduce into this sheet of muscle a transverse darn of fine nylon, No. 5, on a very fine or atraumatic needle. This should provide the type of strong tissue desired, even if some of the muscle fibres should degenerate. The darn is probably more likely to remain fixed and intact than a graft of nylon mesh sewn on the surface, though that is an alternative procedure (Fig. 4). The operation is completed by replacing the gullet into the mediastinum and fixing it in position by fine sutures between cardia and the new hiatus margin. These latter sutures replace the lost phreno-œsophageal ligament. When the gullet is in position, the stomach is automatically restored to its normal subphrenic position and the normal œsophago-gastric angle is also reconstituted.

## RESULTS

In 1955 I reported the results in a series of our cases for posterior repair as follows (Tanner, 1955*a*):

HIATUS HERNIA ALONE

| Posterior repair | Good | Improved | No better |
|---|---|---|---|
| Traced 47 | 31 | 12 | 4 |

Dr. B. F. Swynnerton at St. James' Hospital and Mr. J. E. H. Pendower at Charing Cross Hospital have reviewed the cases I have personally operated on in the last three years, cases requiring a gastrectomy or associated with frank œsophageal stenosis being excluded. The results may be tabulated as follows:

POSTERIOR REPAIR (MAINLY IMBRICATION)

| Number interviewed | Satisfactory | No better |
|---|---|---|
| 16 | 12 (75%) | 4 |

ANTERIOR REPAIR (IMBRICATION AND DARNS)

| Number interviewed | Satisfactory | No better |
|---|---|---|
| 28 | 24 (85%) | 4 |
| (Darns 17 | 15 (88%) | 2) |

10 of the patients operated upon between six months and three years previously at Charing Cross Hospital were X-rayed. Of the 10, 9 were satisfied with their results and none of these showed a hernia by the usual radiographic methods employed, although one still had reflux. The unsatisfactory case had both reflux and a small recurrent hernia on X-ray.

*Contra-indication to Hiatus Repair*

I have mentioned gross œsophageal ulceration and shortening as contra-indications. Obese patients should reduce weight, and maintain the reduction after operation. A difficult case is that in which the lower œsophagus is lined with gastric mucosa. The hiatus may also be weak in such patients. Repair here will make matters worse, but these cases can be excluded by careful pre-operative œsophagoscopy. I would finish by emphasizing that no patient should be operated on without a careful preliminary œsophagoscopy. Carcinoma must be excluded and if abdominal repair is to be undertaken one must be sure that the gullet is mobile and that there is no penetrating ulcer. Penetrating ulcers of the gullet require an abdomino-thoracic approach.

REFERENCES

MERENDINO, K., and DILLARD, D. H. (1955) *Ann. Surg.*, **142**, 486.
TANNER, N. C. (1955*a*) *Lancet*, ii, 1050.
—— (1955*b*) *Ann. R. Coll. Surg. Engl.*, **17**, 103.

**Mr. R. H. Franklin** (London):

The difficulty in treating hiatus hernia is that surgery is called for to deal with the complications which may be the result of the hernia, and these are so varied that they rule out the possibility of a standard operation for all patients. The symptom-free hiatus hernia which is discovered incidentally should not, as a rule, require treatment. The subject is made more difficult by the fact that reflux œsophagitis with all its complications is sometimes seen in patients in whom no hiatus hernia can be demonstrated. Infants constitute a special problem and will not be considered here.

*Symptoms associated with Hiatus Hernia*

The symptoms which lead the patient to seek advice are pain, dysphagia and hæmorrhage, and these symptoms may occur separately and in all degrees of severity. When pain is the only symptom, an attempt should be made to relieve the patient by a conservative regime, the most important thing being to impress on the patient the necessity for avoiding anything which favours regurgitation. Thus, posture to prevent regurgitation must be kept up at night as well as during the day-time, and rather than trying to raise the shoulders on pillows it is often easier to raise the head of the bed. Other factors which tend to increase the abdominal pressure, such as tight belts or abdominal supports, should also be avoided. Weight reduction in the case of obesity is very important. It is only when a thorough course of medical treatment has failed that operation should be undertaken in those patients who are suffering from heartburn as the only symptom and in whom there are no other complicating features present.

*Indications for Operation*

Operation is indicated if there is a marked stricture at the lower end of the œsophagus; if pyloric stenosis is present due to a duodenal ulcer; or if the part of the stomach in the chest has itself developed a chronic ulcer. In all these cases, operation is likely to be the only treatment which will afford the patient any permanent relief. In some patients suffering from duodenal ulcer associated with spasm, pain from reflux œsophagitis may be the presenting symptom if they happen to have an incompetent cardia. If the ulcer of the œsophagus resulting from this is small it may be possible to give complete relief by means of a straightforward abdominal partial gastrectomy directed at the duodenal ulcer. But this method of treatment should not be regarded as sufficiently reliable to effect a cure in those patients who have already developed severe damage to the lower œsophagus, and it has the disadvantage of making any subsequent operations for the strictured part of the œsophagus more complicated. The types of operation which may be required in dealing with reflux œsophagitis and its complications are the following:

*Operation to Improve the Anatomical Arrangement of the Cardia*

This procedure is suitable for patients who have failed to respond to medical treatment and whose main symptom is persistent pain. (A severe fibrous stricture or severe hæmorrhage necessitates more drastic procedures.)

The aim of the operation is to return the stomach to the abdomen and to keep it in place by suturing the phreno-œsophageal ligaments to the undersurface of the diaphragm, at the same time restoring the normal angle of insertion of the œsophagus into the stomach. In addition the vagi are divided with the object of reducing the acidity of the gastric contents; to overcome any ill-effects from the vagotomy and to ensure rapid emptying of the stomach the pyloric sphincter is also divided. This last procedure has the added advantage that it may bring to light the unsuspected finding of a duodenal ulcer or of pyloric obstruction.

The operation is carried out by a left-sided thoracic approach. The lower œsophagus is

inspected after division of the left pulmonary ligament and a radial incision made in the diaphragm from the costal margin towards the hiatal opening, the incision ending just short of the right crus so as not to damage this structure. The stomach and duodenum are inspected and the hernia demonstrated by passing a hand through the hiatus from the abdomen. If the conditions are suitable for carrying out the operation contemplated, the œsophagus is mobilized as far as the root of the lung, the vagi being divided during this procedure. The peritoneum passing from the stomach to the undersurface of the diaphragm is divided. The phreno-œsophageal ligaments are demonstrated and the stomach kept in place in the abdomen by a series of interrupted thread sutures passing between the phreno-œsophageal ligaments close to the œsophagus and the undersurface of the diaphragm. The sutures are all passed before they are tied. It is often possible to restore the angle of insertion of the œsophagus in the stomach either by stitching the fundus to the undersurface of the diaphragm or by a stitch between the stomach and the left edge of the lower end of the œsophagus. The pyloric sphincter is now divided in much the same way as in a Ramstedt's operation. The opening in the diaphragm is closed meticulously using interrupted sutures of thread, having made sure that hæmostasis is complete.

*Total Gastrectomy and Restoration of Continuity by Roux-en-Y Anastomosis*

This is a satisfactory procedure to carry out when there is a marked stricture of the œsophagus associated with a duodenal ulcer. The operation is carried out through a left-sided abdomino-thoracic approach, excising the lowest 4 cm. of the œsophagus together with the stomach. The spleen is normally left undisturbed. Continuity is restored by means of a Roux-en-Y anastomosis bringing the mobilized segment of small bowel behind the transverse colon. It is often convenient to close the end of the small bowel and to make an end-to-side anastomosis with the œsophagus. Great care is taken to approximate the diaphragm to the small bowel to prevent the possibility of development of a diaphragmatic hernia. At first sight this may seem a very drastic procedure to carry out, but for a patient who has a marked stricture of the œsophagus associated with chronic ulceration of the duodenum, possibly with pyloric stenosis, it is the only procedure likely to be of lasting benefit. Provided care is taken to instruct the patient to take small frequent meals and to persist in his taking fat, an improvement in comfort will normally take place after two or three months.

*Excision of Part of the Œsophagus with Restoration of Continuity by making a High Œsophagogastric Anastomosis*

This procedure is called for when there is a considerable degree of œsophageal stricture, possibly situated high up in the chest with a lot of œsophageal shortening, wnile at the same time the rest of the stomach and duodenum are quite healthy.

In this operation, which again can be carried out by the left-sided abdomino-thoracic approach, the stomach is mobilized, leaving the spleen in position, care being taken not to damage the hiatus. The œsophagus is mobilized up to a point above the arch of the aorta, the part immediately behind the arch having to be done blindly, but if this part is healthy the mobilization can be carried out quite satisfactorily from the left side. The œsophagus is divided just above the arch of the aorta and the stump of the œsophagus displaced to the left of the arch and anastomosed to the fundus of the stomach. The pyloric sphincter is divided. The radial incision in the diaphragm is carefully closed as before and having left the hiatus itself intact, it is easy to approximate this snugly to the stomach.

Post-operatively, the patient is advised to guard against regurgitation by paying attention to posture. Provided this precaution is taken there does not seem to be a particular tendency for these patients to develop œsophagitis higher up, but it may be pointed out at this stage that secondary œsophagitis occasionally occurs whatever operation has been done and even after total gastrectomy some patients develop a very brisk alkaline œsophagitis.

*Partial Gastrectomy together with Fixation of the Stump of the Stomach in the Abdomen*

The indication for this is where there is an ulcer of the stomach or duodenum with associated symptoms of reflux œsophagitis, but in which there is permanent damage of the œsophagus in the form of fibrous stricture formation or severe ulceration.

In this operation the approach as before is by a left-sided abdomino-thoracic incision with thorough mobilization of the stomach and preservation of the hiatus. A partial gastrectomy is usually carried out by Polya's method. The remains of the stomach are fixed below the diaphragm by suturing the phreno-œsophageal ligaments to the undersurface of the diaphragm.

**Mr. Vernon C. Thompson** (London):

During the last ten years there has been so much discussion on hiatus hernia and so much divergence of opinion that the problem has become unduly complicated. I think it should be simplified by regarding hernias through the œsophageal hiatus of the diaphragm in the same

way as other hernias. In general, the principles underlying the treatment of hernia are that the contents should be reduced, the peritoneal sac excised, and the defect in the abdominal wall repaired. The fundamental difference between a diaphragmatic hernia and a hernia through the superficial abdominal wall is that the approach to the former is in my opinion best made from above the diaphragm.

There are three types of hiatus hernia:

(1) Sliding.
(2) Para-œsophageal.
(3) Combined.

Like other hernias they may be symptomless but their complications are serious and may lead to the death of the patient.

Strangulation is rare, but hæmorrhage, ulceration and obstruction are not uncommon, and reflux œsophagitis is a particular complication. These complications are sufficiently common to justify a radical repair in all patients with symptoms unless there is some special contra-indication. The need for operation is determined by the patient who is the best judge of the severity of the symptoms.

To the question whether the operation can be carried out successfully without appreciable morbidity or mortality, my answer is that it can. In the 55 patients on whom I have operated there have been no deaths. The ages range from 6 months to 77 years and many of the cases have been complicated. Since 1950, with an improved technique, I have had only one recurrence. In 2 cases, a sleeve resection for a penetrating gastric ulcer was carried out in addition to the repair. In others the œsophagus was densely matted to the mediastinal structures and in 2 there was an ulcer penetrating the pericardium. In my view there is no place for palliative physiological operations on the stomach done below the diaphragm for this condition. The most severe œsophagitis that I have ever seen was in a patient who had had a subtotal gastrectomy. The lower half of the œsophagus was raw and bleeding so much that the patient's life could only be maintained by frequent blood transfusions. This patient was treated by total gastrectomy and œsophago-jejunostomy using a Roux loop. Another patient who had had a gastro-enterostomy was bleeding to death from a jejunal ulcer. The jejunal ulcer was situated in his chest. In addition to repairing his hernia it was necessary to undo the gastro-enterostomy and resect the jejunal ulcer. Provided the œsophagus has not become too short as a result of fibrosis to allow the hernia to be repaired, there seems to me to be no serious difficulty in dealing with hiatus hernia. The essential points in the technique are that after reduction of the hernia, the œsophagus should be anchored below the diaphragm and the defect in the hiatus should be repaired by approximating the right and left crura of the diaphragm behind the œsophagus. If the hernia is satisfactorily repaired reflux œsophagitis will soon cure itself and strictures can usually be successfully treated by dilatation. The most satisfactory method of treating a stricture is by self-bouginage with gum elastic bougies. This applies to children as well as adults.

The difficult problem in dealing with hiatus hernia occurs when the œsophagus has become so shortened by fibrosis that reduction and repair become impossible. The cases in which the lower œsophagus is lined by gastric mucosa fall into the same category. There are two possible lines of treatment. One is the avoidance of decubitus, the sucking of alkali tablets, and self-bouginage; the other is resection. The first line of treatment is only palliative, and often disappointing. If the stricture is dilated it permits greater reflux and tends to increase the œsophagitis with its complications of pain and hæmorrhage. Resection is drastic but sometimes essential. Resection of the stricture with a low œsophago-gastrostomy on the left side of the chest is unsatisfactory as it merely reconstitutes the original cause of the œsophagitis. If, however, the anastomosis is made high up above the arch of the aorta on the right side of the chest so that the fluid level in the stomach is well below the level of the anastomosis, no regurgitation or œsophagitis occurs. The alternative is to use a loop of the jejunum or colon to replace the lower end of the œsophagus. I have had no experience of using the colon for this purpose and I am not satisfied that the jejunum is entirely satisfactory, because the type of peristalsis in the loop is not a forward emptying movement but one of to-and-fro mixing so that the œsophagus above the anastomosis is constantly bathed in digestive secretions. These secretions may not be as irritating as pure gastric juice but nevertheless they have digestive properties. I discovered this years ago when using subcutaneous jejunal loops for high resections of the œsophagus in carcinoma. I have seen œsophagitis and stricture develop after total gastrectomy and œsophago-jejunostomy with a Roux loop. Although one is naturally reluctant to put most of the stomach in the chest, especially in a child with the hope of a normal lifetime, I have yet to see œsophagitis or stricture in a really high œsophago-gastric anastomosis. These children eat and live normally. My present practice, therefore, when resection is necessary is to mobilize the stomach through an abdominal incision and bring it up for a high anastomosis through a right thoracotomy.

**Mr. Donald Barlow** (London):

In this problem, the first essential is an accurate diagnosis, and the exclusion of other conditions such as carcinoma, and achalasia. For this purpose I use a high-power distally illuminated telescope (Fig. 1). With this instrument there is a brilliantly lit close-up view and accurate biopsy is also possible. Hiatus hernias are common in those past middle life especially if they are fat and corseted. Many patients can be treated conservatively. They must discard their corsets, avoid stooping, and avoid recumbency at night. For this latter purpose, I advise the use of a specially upholstered bed chair (Fig. 2).

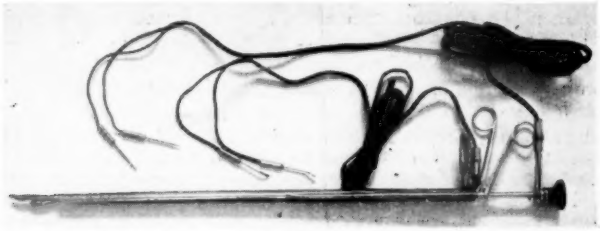


FIG. 1.—Barlow's high-power distally illuminated œsophageal telescope.



FIG. 2.—Upholstered bed chair to prevent gastric contents entering œsophagus and lungs at night.

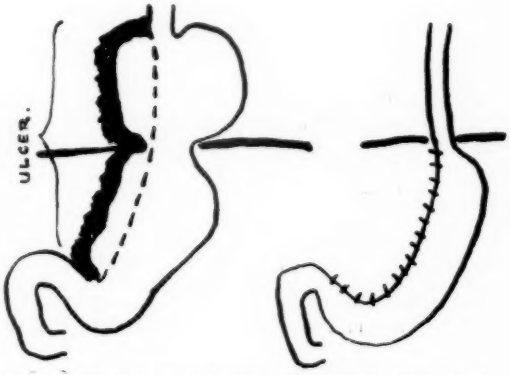



FIG. 3.—Method of repair when huge gastric ulcer extends into hiatus hernia.

*Hernias Requiring Operation are:*

(1) Those in children and young people. This is necessary to prevent ulceration and stricture later in life. Good repair can be effected via the abdomen because, since there is no ulceration, reduction is easy and the limbs of the right crus are easily defined for suture.

(2) Those with œsophago-gastric ulceration with or without stricture. Because of adhesions, the operation must be through the chest and full mobilization obtained. If mobilization is attempted via the abdomen, the risk of leakage and empyema is grave. In the repair of a simple hernia, it is usually possible to preserve the vagi, and there is no post-operative pylorospasm. If there is ulceration, both vagi may be destroyed, and pyloroplasty or gastro-enterostomy through the diaphragm is advisable after the repair.

(3) Those with associated gastric or duodenal ulcers. Pyloric stenosis and gastric or duodenal ulcers are often missed. Insufficient barium may pass to demonstrate these lesions owing to the dysphagia. Duodenal ulcer with varying degrees of pyloric stenosis exists in about 20% of hernias with ulceration at the cardia.

The approach in these cases is either through the chest and diaphragm as in (2), or by a thoraco-abdominal incision. The following alternative procedures may then be performed:

(*a*) Repair plus gastro-jejunostomy.

(*b*) Splitting and opening of the œsophageal muscle, intramuscular resection of the ulcer and stricture with mucosal anastomosis and repair of muscle, followed by gastro-jejunostomy.

(*c*) Resection of whole stomach including the ulcers at pylorus and cardia and followed by a Roux-en-Y anastomosis. Polya gastrectomy is rarely indicated.

When there is a gastric ulcer extending into a hiatus hernia, the condition can be cured through the abdomen without thoracotomy. After "cracking" the ulcer off its bed which is left, the hernia is easily reduced. The ulcer edges are then excised and sutured to make a tubular stomach (Fig. 3).

(4) Those with very large hernias with pain due to volvulus or smaller hernias with pain and discomfort due to the trapping of wind. In this group are patients with tachycardia.

"Spill-over disease", i.e. aspiration infection of the lungs is more common than is supposed, occurring in all types of chronic œsophageal or pyloric obstruction. Its presence constitutes a strong reason for operation.

(5) Those with carcinoma in a hiatus hernia. Radical thoraco-abdominal surgery with Roux-en-Y repair is usually indicated.

(6) Children and even young babies may have hiatus hernias. These should be repaired at an early age. Only too often they present when ulceration and stricture have resulted in prolonged malnutrition and even rickets and scurvy. These patients demand great care and patience. Dilatations over a long period may have to be performed but surgery should not be unreasonably delayed. A child's œsophagus may appear grossly shortened but when the ulcer is freed, it is amazing how the œsophagus can be extended.

[*November* 6, 1957]

THE following Specimens were shown:

(1) **Two Cases of Recurrent Crohn's Disease Following Right Hemicolectomy.** (2) **Ileitis and Right-sided Colitis Treated by Two-stage Ileo-pelvic Anastomosis and Subtotal Colectomy.** (3) **Recurrent Ulcerative Colitis Following Ileo-rectal Anastomosis and Colectomy.**—Mr. E. C. B. BUTLER.

**Regional Colitis.**—Mr. J. T. RICE EDWARDS.

**Calculus of the Appendix.**—Mr. R. E. SHAW.

(1) **Infarcted Lymphangioma Involving the Colon of an Infant.** (2) **Adeno-carcinoma of Thyroid in a Girl Aged 12.**—Mr. P. A. LANE-ROBERTS.

**Proximal Two-thirds of Stomach to Show Gastro-œsophageal Varices, Resected 1949** (the patient attended the meeting).—Mr. RONALD MCGRIGOR (for Mr. ALAN HUNT).

**Carcinoma in Achalasia of Œsophagus.**—Mr. KENNETH OWEN.

**Abdominal Aneurysm Causing Duodenal Hæmorrhage.**—Mr. J. E. H. PENDOWER (for Mr. NORMAN TANNER).

**Carcinoma of the First Part of the Duodenum.**—Mr. C. Q. HENRIQUES (for Mr. H. C. EDWARDS).

**Chronic Pancreatitis Treated by Pancreatectomy** (three specimens).—Mr. RODNEY SMITH.

**Grass Seed as Cause of Recurrent Hæmoptysis.**—Mr. A. E. WHEATLEY (for Mr. W. P. CLELAND).

**Failure of Development of the Müllerian Ducts with Torsion of a Rudimentary Uterus.**—Mr. P. E. B. HOLMES (for Mr. A. J. HERIOT).

(1) **Chordoma of Frontal Region.** (2) **Parathyroid Tumour.** (3) **Pre-sacral Cyst.** (4) **Solitary Cyst of Thyroid.** (5) **Carcinoma in Benign Peptic Ulcer.**—Mr. A. E. CARTER (for Mr. A. DICKSON WRIGHT).

**Ossification in Fibro-adenoma of the Breast.**—Mr. A. J. HERIOT.

## BOOK REVIEWS

**An Introduction to Psychopathology.** By D. Russell Davis. (Pp. viii + 388. 30s.) London: Oxford University Press. 1957.

It is refreshing to read a book on psychopathology which is not a formal recitation of Freud's theories. The author has worked in both a psychological and a clinical framework, and this book is the logical outcome of applying his experience in the first to the problems he met in the second. The exposition is clear, and full without being repetitive. The chapter on disorders resulting from brain lesions is particularly good. There are few criticisms to be made except perhaps that cross-laterality should be discussed in the section dealing with handedness; and that the association of stammering with left-handedness is not as certain as is suggested.

The usefulness of a book of this standard is immediately apparent in more than one context. It is clear enough to be understood by clinical psychologists, and indeed is an expansion of lectures given to undergraduate students of psychology. It should be a most helpful book to the medical student who is beginning psychiatry, and is sometimes unable to see what connexion his clinical studies have with the lectures given to him previously by an academic psychologist. It deserves a much wider public than this, however, for it shows the cornerstones of twentieth century psychiatry, and puts in perspective, without heat or bias, the sad determinist philosophy which once was all we had.

The book is agreeably produced and has an excellent index.

**The Evolution of Medical Education in the Nineteenth Century.** By Charles Newman, M.D., F.R.C.P., Dean of the Postgraduate Medical School of London. (Pp. 340. 30s.) London: Oxford University Press. 1957.

In medicine as in politics we are all heirs of, and often prisoners of, our history. This fascinating and erudite book on medical education in the nineteenth century appears therefore at a most opportune time when the way is open, as a result partly of the compulsory preclinical year, partly of the new regulations of the General Medical Council, for greater freedom for experiment in the content and technique of medical education. No one who is concerned with such experiments can afford to ignore this book. All could read it with profit. That is not to say that it is all gold and no dross—this would be too much to ask. But for the gold first.

The first 133 pages are medical history at its best, and delightful reading. The author starts with an account of medical education and practice in England at the beginning of the nineteenth century. Staggering to the modern mind is the extent to which physicians relied on symptoms to the almost total neglect of physical signs. This is so well described and illustrated that it is easy to appreciate the greatness of the revolution in medicine initiated by French pathologist-physicians with Bichat and Laennec as the leaders, when they introduced the science of clinical signs controlled by morbid anatomical findings. This paved the way in this country for the discoveries of the great Guy's physician- and surgeon-pathologists of the early and middle years of the century.

The real, though limited, advance in medical education that the Apothecaries Act of 1815 meant is well brought out. It is interesting to note that at this time five-sixths of the general practitioners of the country were surgeon-apothecaries, and that the College of Physicians by its unwise attitude to the 1815 Act cut itself off from general practitioner education for half a century. Of outstanding interest also are the extensive extracts from the Guy's clinical notes from 1823 to 1865, and the author's opinion of the importance in medical education of Students' Clinical Societies. Mention is made of the formation of the Guy's Clinical Society in 1836 and the Abernethy Society at Bart's in 1832. There is no note, however, that the oldest student medical society in London was formed by students of the Middlesex in 1774 "at the expense of their own candles".

After the brilliant opening comes a long dull patch from page 134 to page 193 dealing in detail with the prolonged tussles and the 17 Bills introduced before the final passage of the Medical Act of 1858. The later chapters on the ideal of the "safe general practitioner" which had such a profound influence on medical education, and on the rise of laboratory medicine are again very good, but both author and reader have by now lost some of their *élan*. When the book comes to a second edition, it would benefit by a drastic curtailment of the intermediate dull patch, and also by the elimination of the many asides and appendices giving the view of the author on topical subjects, which, however important, are not history. If this were done, the book would certainly become a classic in the literature of medical education.

**The Quicksilver Doctor. The Life and Times of Thomas Dover, Physician and Adventurer.** By Kenneth Dewhurst. (Pp. ix + 192; illustrated. 21s.) Bristol: John Wright & Sons Ltd. 1957.

The picturesque and belligerent personality and the colourful life of Thomas Dover have formed the subject of many articles, including one by Sir William Osler. The first full-length biography in book form, by a distinguished novelist, Mr. L. A. G. Strong, appeared in 1955. This new biography by a medical writer is elegantly and entertainingly written, is fully documented with footnotes, quotations from chronicles, diaries, manuscripts, and other sources, and contains much new material. The story is skilfully presented against the background of the times: the state of medical practice; the quack and his nostrums; such great contemporary figures as Richard Mead (and his indecorous scuffle with John Woodward in the courtyard of the College of Physicians), Sir Samuel Garth, John Radcliffe, Sir Hans Sloane, Barton Booth the tragedian, John Freind. In the chapter entitled "Birth of a Legend", the author takes pains to explain that the famous expedition to the South Seas which Dover helped to finance and in which he played a leading rôle, "was in no sense a buccaneering adventure or a piratical cruise", and he accuses other writers of having distorted this aspect of Dover's career. "Dover's powder", a household remedy for two centuries that has survived in modified form to-day, was first mentioned in his book bearing the grandiloquent title "The Ancient Physician's Legacy to his Country, being what he has collected in Forty-Nine Years' Practice . . ." (1732). Its pages are liberally spiced with bizarre details of his travels and flavoured with anecdotes of doubtful authenticity. There is a good description of the iliac passion (appendicitis), for which oral quicksilver and purging are recommended, and one "revolting prescription" for asthma. Other chapters in Dr. Dewhurst's book deal with "The Rescue of Selkirk (Robinson Crusoe)", "The Quicksilver Doctor", and "Dr. Dover and his Critics". The volume concludes with an 8-page bibliography of manuscripts in the Public Records Office, the House of Lords, the British Museum, the Bodleian Library, &c., and of books and articles.

**The Clinical Management of Varicose Veins.** By David Woolfolk Barrow, M.D. (Pp. xiii + 169; illustrated. 45s.) London: Cassell & Co., Ltd. 1957

Varicose veins and their complications are so common that it is to be expected that many books would be written about them. The fact that this book has gone into a second edition suggests that it has been found useful. The preface does not state for whom it is intended but it seems to be most suitable for those who are training to become surgeons. After a short historical introduction, the relevant anatomy and physiology are described and clearly illustrated. With them there is an account of the ætiology of the condition. The chapter on pathology deals only with the changes occurring in the veins and does not mention the complicating abnormalities which may occur in the skin. After an account of the examination of the patient, there are four chapters on treatment. The last three chapters deal with complications, thrombophlebitis, and prophylaxis and after-care. The bibliography occupies eight pages but, surprisingly, Martorell and Anning are both omitted. There is a good index. Except for the chapter on complications this is an excellent book. The treatment described is orthodox and is set out very clearly with many helpful diagrams but the author should have obtained the help of a dermatologist in writing the chapter on complications. The mythical condition, varicose eczema, is described but with no idea suggested as to why or how it occurs. Bisgaard's treatment for the ulcerated leg is not mentioned. There are many photographs, most but not all of which are good. It can be recommended to young surgeons with the warning that they should ignore the section relating to the skin.

**British National Formulary 1957.** (Pp. 226. 6s. 6d.) London: The British Medical Association and The Pharmaceutical Press 1957.

The fourth edition of this useful, conveniently sized and inexpensive manual, prepared by the Joint Formulary Committee representing the medical and pharmaceutical professions, contains the word "British" in its title, to distinguish it from the U.S.A. National Formulary. Additions, deletions, and amendments are listed on pages 8–10. The section on poisoning in "Notes for Prescribers" includes a monograph on agricultural poisoning, and a note on drug addiction has been added. We are glad to see that "tonics" have been retained. The Formulary itself consists of three sections: general, infants' (on pink paper), and dental practitioners'. An appendix lists proprietary preparations. It is emphasized that a doctor is free to prescribe what he considers to be in the best interests of his patient, whether or not the preparation appears in the British National Formulary. The comprehensive index (22 pp.) is a model. Interleaved copies of this book can be obtained at 10s.

[*Continued on p.* 53

# Section of Odontology

President—J. A. S. WRIGHT, A.F.C., F.D.S. R.C.S.Eng., H.D.D., F.D.S. R.C.S.Ed.

[*February* 27, 1957]

Continued from September *Proceedings*, 1957, p. 677

## A New Method of Demonstrating the Retention of Foodstuffs in the Mouth, with Special Reference to Different Forms of Sweets

By ALEXANDER B. MACGREGOR, M.A., M.D., B.Chir., M.R.C.S., L.R.C.P., F.D.S. R.C.S.

*Professor of Dental Surgery and Director of Dental Studies, University of Birmingham, England*

### FOREWORD

THE relationship between the consumption of carbohydrates, particularly refined sugars, and the dental caries rate has been stressed for many years and a great deal of work has been done on the subject, e.g. Toverud (1949), Sognnaes (1949), &c. The work of Stones and his collaborators (1955), however, indicates that merely adding sugar to the diet may not, of itself, increase the caries rate. A careful review of the literature suggests that the quantity of carbohydrate may not be as important as the form in which it is taken. Thus, Bibby, Goldberg and Chen (1951), estimating the amount of sugar in the rinsing fluid after spraying the mouth, showed a very considerable difference in the retention time in the mouth of different forms of carbohydrate. More recently Lundqvist (1952), after showing that a high sugar concentration in the saliva associated with delayed clearance time is associated with greater caries activity, came to the conclusion that candies, particularly toffees and caramels, not only gave a delayed sugar clearance from the mouth but were also associated with a very high caries rate in clinical experiments.

The amount spent on sweets in this country amounts to approximately two hundred and thirty-five million pounds each year (£255 millions 1956), and the average consumption per head of population is 8 oz. a week. This rate of consumption is the highest in the world and should be compared with an average consumption per week of 5 oz. in the United States and Australia, 4 oz. in Canada, slightly over 3 oz. in Sweden and 3 oz. in France.

A possible association of this consumption of sweets, particularly toffees, with a high caries rate, has been suggested, though on somewhat nebulous grounds, for many years. It was, in consequence, thought by the author that it would be of interest if an experimental method could be found by which differing times of retention of varying forms of confectionery and foodstuffs could be demonstrated.

### EXPERIMENTAL TECHNIQUE

Many substances were tried as "indicators" but the choice was somewhat limited owing to certain prerequisites. These were:

(1) Freedom from any toxicity.
(2) Insolubility in water or saliva to obviate possible errors due to diffusion.
(3) Small particle size.
(4) Easy recognition both macroscopically and microscopically.
(5) Stability to withstand destruction during any processes involved in the manufacture of foodstuffs and incorporation of the indicator, e.g. boiling.

Iron oxide powder was tried in the first instance but while this could be used on teeth to be extracted it was unsuitable for use in tracing foodstuffs round the standing teeth as the potassium ferrocyanide used to reveal the iron by the Prussian blue reaction could not be used in the mouth owing to its poisonous nature. The use of iron oxide powder gave encouragement, in that foodstuffs could be traced in fissures, for example; but apart from the major drawback already mentioned, other sources of error were soon found such as iron being already present from medicine or other sources, and also the occasional presence

of iron in the dentine immediately in advance of softening due to caries, where present. The presence of iron in this position although not germane to the experiments under discussion is of considerable interest, and further work is being done to try to elucidate the reasons for its presence.

Aniline dyes were discarded owing to toxicity. X-ray opaque materials were insufficiently accurate for checking disposition, and diatomaceous earth proved unsuccessful owing to the characteristic shape of the diatoms being lost after boiling. Dyes used for the colouring of foodstuffs were tried, but even the reputedly least soluble of these showed sufficient solubility to vitiate the results. After much experimental work along these and other lines an approach was made to the technical division of Imperial Chemical Industries who most kindly supplied, after further experimentation, a suitable dye in the form of specially purified copper phthalocyanin. This dye is pharmacologically inert, completely insoluble in water, is of fine particle size and bright blue in colour.

In the first instance it was decided to work with three different but typical forms of sweetmeat, e.g. boiled sweets, chocolate and toffee. Early experiments in trying to incorporate dyestuffs in home-made toffees in the laboratory, merely revealed the self-evident fact that we lacked both the skill and the knowledge to indulge successfully in the refinements of the manufacture of confectionery. A very large firm of confectionery manufacturers was, in consequence, approached, and their most generous and valuable co-operation is warmly appreciated. Toffees, chocolates and boiled sweets containing the dyestuff have been made for us whenever required, and without this very great help the work would not have been possible.

The experimental work has been divided into two phases, in the first of which dental students were asked to chew toffees, chocolates, and boiled sweets on different occasions and photographs were taken at selected intervals. In addition, a cinematographic film has been taken to record the results.

In the second phase, patients about to have a tooth extracted in the premolar or molar areas chewed a toffee over this tooth before the tooth was extracted. Care was taken to see that these teeth were not grossly carious and as far as possible those showing no caries or only very small carious lesions were selected.

## Results

In the first phase in a random sample of 20 subjects, toffee was seen adhering round fissures interstitially, and cervically, in the area where toffee was chewed in large amounts easily capable of photographic recording five minutes after finishing the toffee (Fig. 1). After twenty minutes this toffee was still present and still in quantities capable of photographic recording, particularly interstitially and cervically (Fig. 2). One hour after the toffee had been consumed it was still possible to record the toffee photographically in many mouths (Fig. 3) but even if not capable of good photographic recording it was easily visible on careful inspection in 17 of the subjects.

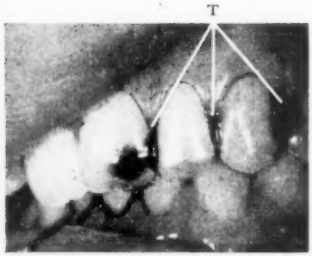



Fig. 1.—Mouth five minutes after chewing toffee.

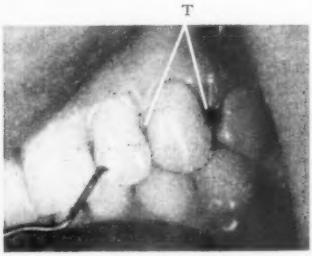



Fig. 2. — Same mouth twenty minutes after chewing toffee.

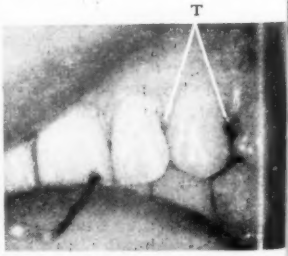



Fig. 3.—Same mouth sixty minutes after chewing toffee. T = toffee in each case. N.B.—More toffee was stuck between and around the posterior teeth but the anterior teeth were chosen for photographic convenience.

These results refer to toffee that could be seen and photographed, or seen, i.e. to toffee present on the surface. It is reasonable to suppose that where toffee could be seen, far more was probably present unseen between the teeth and in many instances where it was not seen there was, in fact, some present interstitially or in fissures and cavities.

A similar method has been used with copper phthalocyanin dye contained in milk

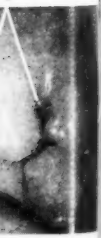


PLATE I (Figs. 4–8)
M. CGREGOR—*Odontology*

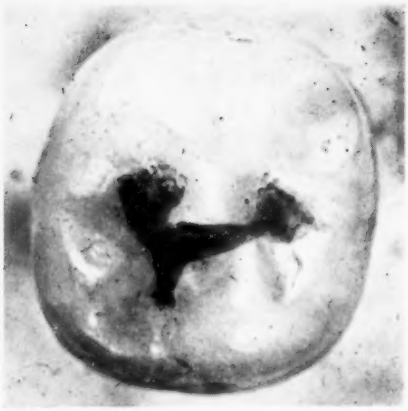


FIG. 4.

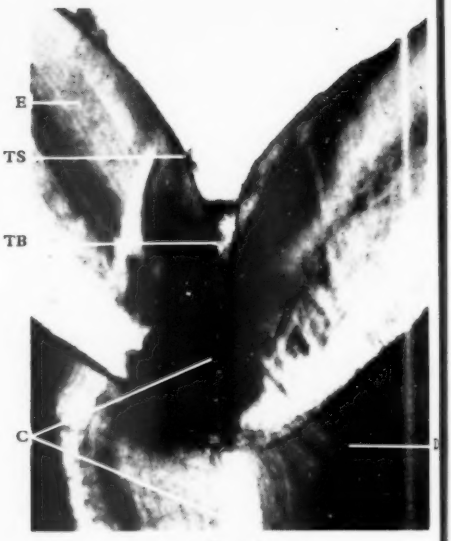



FIG. 5.




FIG. 6.

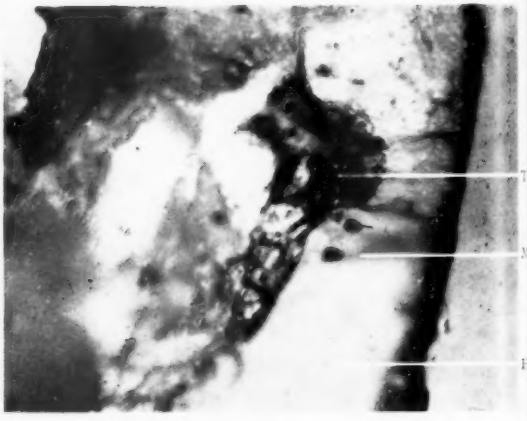


FIG. 7.

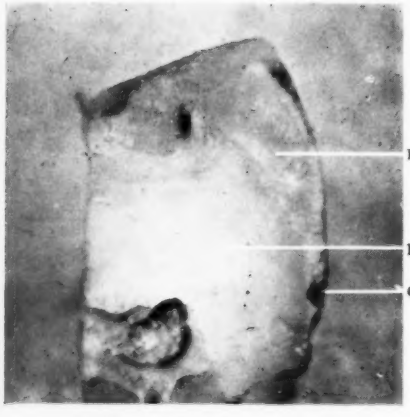



FIG. 8.

FIG. 4.—Lower biscuspid tooth extracted shortly after chewing toffee over it showing pattern of toffee in and around the fissures.

FIG. 5.—Ground section of molar tooth extracted shortly after chewing toffee over it. Toffee can be seen on the sides, and wedged at the base, of the occlusal fissure. The relationship of the carious lesion in the enamel and dentine to the base of this fissure is of interest, E=enamel, D=dentine. TS=toffee on sides of fissure. TB=toffee at bottom of fissure. C=carious process in enamel and dentine.

FIG. 6.—Higher magnification of a similar specimen to that shown in Fig. 5. E=enamel. TS=toffee on sides of fissure. TB=toffee at bottom of fissure.

FIG. 7.—Molar tooth with interstitial cavity after toffee chewing showing how toffee has been squeezed down between the contact points into the cavity. E=enamel. MC=lower margin of cavity. T=toffee.

FIG. 8.—Premolar tooth with small cervical lesion showing how toffee has been squeezed into this by the chewing action. E=enamel. D=dentine. CC=shallow cervical lesion containing toffee.

chocolate and boiled sweets, the chocolate and boiled sweets containing approximately the same concentration (1%) of phthalocyanin dye as was present in the toffees. While the distribution in the mouth after chewing appeared very much the same with all three materials, a great difference was found in the *time* of retention of toffees compared with both chocolate and boiled sweets. A few minutes after chewing the appearance of the teeth was very similar with chocolate and toffee, though the amount of chocolate seen interstitially was not so great as when toffee was used. Boiled sweets gave a similar distribution picture, but the amount adhering was not so great as in the case of the chocolate and far less than that seen with the toffee. Twenty minutes after chewing a very great difference was revealed. In only 5 of the 20 subjects slight traces of chocolate containing the dye were seen and a very slight trace only, seen in 2 subjects after boiled sweets. The amounts present were not capable of photographic recording and were not comparable with the amounts seen after toffee. One hour after chewing one subject showed a slight trace of chocolate revealed by the dye but no subject showed any trace of boiled sweets at this time. There was in fact a marked contrast between the appearance seen after toffee one hour after chewing and the appearance seen either after chocolate or boiled sweets.

In the second phase extracted teeth over which toffee had been chewed when still *in situ* were firstly examined by reflected light with a dissecting microscope. An interesting pattern of toffee was frequently revealed outlining the fissures and extending down into them (Fig. 4). These teeth were then split along the fissures and again examined with a dissecting microscope. Ground sections were then prepared, care being taken to see that the direction of rotation of the wheel was away from the bottom of the fissure to guard against the possibility of any loose stained toffee material being forced into the fissure by the grinding process. A typical section of such a tooth is shown in Figs. 5 and 6 from which it can be seen how deeply traces of toffee can be found in these fissures. It was of interest that in many instances where small interstitial cavities were present the toffee had been forced into these cavities after being squeezed between the teeth (Fig. 7) and traces of toffee were even found in shallow cervical cavities (Fig. 8).

To control the possibility that the presence of blue dye was not necessarily associated with the presence of toffee, sample scrapings were taken from subjects in the Phase I experiments and tested for sugar. Even in those subjects where the dyestuff was present one hour after chewing, the dye was found to be associated with sugar when tested by the rapid furfural method. A further possibility that sugar was already present between the teeth before chewing was eliminated by taking samples of food debris from interstitial areas between the premolar and molar teeth and testing them for the presence of sugar. It was of interest in this connexion that one subject who was tested at 3 p.m. gave positive results. After questioning it was found that one hour and a half before, he had finished his lunch by eating a bar of confectionery made of stiff caramel toffee covered with chocolate.

AUTHOR'S NOTE.—For reasons of cost the original colour photographs cannot here be reproduced. Black and white prints failed to differentiate the blue toffee from other dark tones, and by the kindness of the Editors the present compromise has been reached. The somewhat artificial appearance of the illustrations is due to blue ink having been applied to the black and white prints. The position and extent of this blue ink does, however, correspond to the position and extent of the blue coloration in the original colour photographs.

A. B. MACG.

## DISCUSSION

The work done so far is insufficient to allow final conclusions to be reached. Further work is continuing on more subjects and with the use of different types of confectionery and foodstuffs.

Certain conclusions can, however, be drawn from the work so far done.

(1) The incorporation of blue copper phthalocyanin dye in foodstuffs offers a method by which the disposition of foods in relation to teeth can be tested. It is sufficiently stable and colourful to allow photographic reproduction of both macroscopic and microscopic results.

(2) It would appear from the results so far obtained that chewing of toffee results in very considerable quantities being retained in and around the teeth for considerable periods, in many instances over one hour after chewing.

(3) There appears to be a very considerable difference in both the quantity and time of retention between toffee on the one hand, and chocolate and boiled sweets on the other.

(4) The chewing of a toffee results in many instances in parts of it being forced into the

fissures, even when these are small, and it seems probable, especially in view of the experiments in Phase I, that rapid dissolution and removal from such sites as these fissures is unlikely. The presence of the toffee in small interstitial cavities and even in cervical ones is also noteworthy.

These results assume particular significance in view of the known rapidity with which sugar solutions in the mouth can produce acid. They also are in marked agreement with the results given by Lundqvist for the Vipeholm experiments, in which it was shown that both the caries incidence and the sugar clearance time from the mouth, particularly the former were far higher for toffees and caramels than for the other foodstuffs and sweets given to children during the experiment (Figs. 9, 10).

| Study groups | Sugar clearance | | Dental caries | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Number of patients | Time % of day Mean | Approx. time years | Number of patients | Non-carious surfaces at the beginning of Study | | Surfaces becoming carious during Study | |
| | | | | | Total | per person | Total | per person per year |
| Bread .. | 6 | 8·9 | (4)2 | 41 | 2,246 | 54·8 | 107 | 1·30 |
| Control .. | 24 | 10·1 | 4 | 60 | 3,544 | 59·1 | 71 | 0·30 |
| Sucrose .. | 19 | 13·5 | 4 | 57 | 3,123 | 54·8 | 153 | 0·67 |
| Chocolate | 32 | 23·5 | 2 | 47 | 2,412 | 51·3 | 110 | 1·17 |
| 8 Toffee .. | 29 | 24·7 | 3 | 40 | 2,708 | 67·7 | 375 | 3·13 |
| Caramel .. | 36 | 34·9 | 2 | 62 | 3,585 | 57·8 | 306 | 2·47 |
| 24 Toffee | 5 | 57·8 | 2 | 48 | 2,892 | 60·3 | 386 | 4·02 |

FIG. 9.—Figures giving sugar clearance times and dental caries activity for differing forms of foodstuffs.

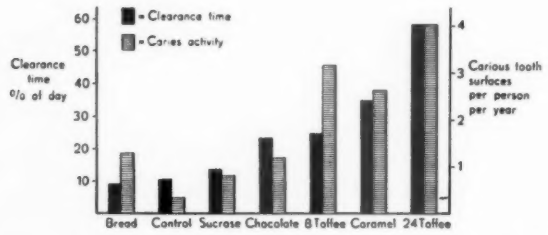



FIG. 10.—Figures giving sugar clearance times and dental caries activity for differing forms of foodstuffs.

[Figs. 9 and 10 are taken from (1952) *Odontologisk Revy*, **3**, suppl. 1, Fig. 9, p. 80, Fig. 10, p. 82. Oral Sugar Clearance and Its Influence on Dental Caries Activity, by Claes Lundqvist; by kind permission.]

In conclusion, I wish to record my great appreciation of the help given by members of the staff and students both at the University and at the Dental Hospital at Birmingham. I would particularly like to thank my colleague Dr. Marsland, and Mr. Johnson of the University Technical staff for their assistance with photography, and Mr. Lees of the University Technical staff for his patience and enthusiasm in preparing split and ground sections of teeth.

## REFERENCES

BIBBY, B. G., GOLDBERG, H. J. V., and CHEN, E. (1951) *J. Amer. med. Ass.*, **42**, 491.
LUNDQVIST, C. (1952) *Odont. Revy*, **3**, suppl. 1, 5.
SOGNNAES, R. F. (1949) *Brit. dent. J.*, **87**, 291.
STONES, H., *et al.* (1955) Report No. 288. Medical Research Council.
TOVERUD, G. (1949) *Proc. R. Soc. Med.*, **42**, 249.

*Proceedings of the Royal Society of Medicine* Vol. 51 45

# United Services Section

President—Sir CECIL WAKELEY, Bt., K.B.E., C.B., F.R.C.S.

[*October* 3, 1957]

## The Problem of Noise in the Royal Air Force

By Wing Commander P. F. KING, F.R.C.S.Ed., D.L.O., and
Flight Lieutenant R. P. GANNON, B.Sc., M.B., Ch.B.

*Department of Otorhinolaryngology, and R.A.F. Acoustics Laboratory, Central Medical Establishment, Royal Air Force*

### INTRODUCTION

IN the Royal Air Force, as in the other Services, and indeed in industry, noise is a problem which has to be tackled principally because of its effects on personnel. In this paper, the problem of noise in the Royal Air Force will be discussed with an eye on circumstances which are largely peculiar to the Royal Air Force; the damaging effects of artillery noise will not be included, as the noise hazard from arms of all calibres is a problem which is common to all three Services. Broadly speaking, exposure to noise for any length of time will produce both fatigue in the individual with lessened work efficiency, and fatigue of the organ of hearing. Finally, if the insult is repeated often enough and for long enough, auditory fatigue will become converted into persistent perceptive deafness. The production of perceptive deafness in boilermakers was described in the middle of last century, but it was known long before that exposure to noise produced deafness under certain circumstances.

We propose to deal principally with the noise of aircraft engines and the effect of this noise on people in different situations, but we shall also consider ancillary equipment in the same light. Experience has shown that with the constant search for more advanced aircraft, of higher ceiling and greater speed, the power of the engine has increased and with it the noise output.

### NOISE MEASUREMENT—ANALYSIS—ASSESSMENT

Noise measurements are made in order to assess the risk to hearing. The difference between the noise level measured and that believed to be safe is the noise reduction required. The subjective effect of a noise depends on its frequency composition, different frequencies having different effects, certain frequency ranges being heard more easily than others. Other frequency ranges, not necessarily the same, are more damaging to the hearing. The relationship between noise level, frequency, and duration and the resultant effect is extremely complicated so that instruments are not available to give a single figure for the subjective effect of a noise. Instead we measure the total sound level, the variation of level with frequency, and the duration. In practice the sound is divided into frequency bands and the graph of variation of level with frequency is known as a frequency analysis. The subjective effects may then be assessed from these results.

Noise levels are usually quoted in decibels, sound pressure level and the decibel is a LOGARITHMIC measure of the RATIO of the POWER of the sound measured to that of some standard sound level. The subjective effect of noise is more akin to this logarithmic scale than to a linear one.

Typical noise levels are:

| | |
|---|---|
| Near jet aircraft at full power .. | 130 db. s.p.l. |
| Underground railway .. .. | 100 db. s.p.l. |
| Conversation .. .. .. | 65 db. s.p.l. |

From the results of the noise measurement an assessment of the noise hazard may be made.

## Noise Hazard: Assessment of Risk

The assessment of the risk of permanent hearing loss from noise has been studied by many workers, in many fields. There remains, as yet, no definite agreement on what constitutes dangerous noise and any assessment is to some degree a matter of conjecture and personal opinion. However, the weight of experimental evidence required to give a definite answer is gradually being accumulated, but the very nature of the task makes this a prolonged study.

Kryter (1950) concluded from his own studies and those of other workers that the maximum safe intensity at which no deafening effect will occur is probably in the neighbourhood of 85 db. s.p.l. per critical band for long periods of exposure applied intermittently over months or years. He suggested that, for brief exposures lasting up to one hour, the level could be raised to 100 db. per critical band. He also made it quite clear that *a noise must be analysed before its deafening value can be estimated.*

Parrack (1951) proposed a deafness risk criterion, which showed that he considered the safe level to be 95 db./octave band or less for a wide range of frequencies. Slightly higher levels were allowed at the very low frequencies.

Rosenblith *et al.* (1953) in a comprehensive study of the problem of noise and man defined what they termed the "damage risk criterion", not only in terms of frequency and intensity, but also of exposure time and character of the noise under consideration. This criterion was adopted later in 1953 by the Benox Group (1953) as their reference standard and has since found wide acceptance. It is shown in Fig. 1. It was put forward

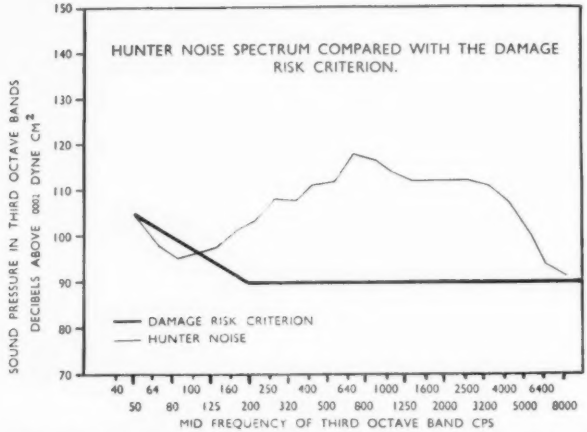



Fig. 1.—The noise spectrum of a Hawker Hunter Fighter compared with the "damage risk criterion" of Rosenblith *et al.* (1953).

with qualifications defining the character, duration, and intensity of the noise—but is considered to be safe for a working lifetime of exposure.

A more recent study of the damaging effect of noise was made by the Exploratory Subcommittee Z24-X-2 of the American Standards Association in their report published in 1954. This implies a criterion lower than that proposed by Rosenblith and his colleagues, but which is not so general in its application and has not received such wide acceptance. It cannot be applied in the assessment of aircraft noise—as the frequency analyses of the noise do not lie within the limits on which the criterion is based.

The noise under consideration is therefore measured, recorded and analysed, and data recorded about exposure time and character of the noise. This analysis is then compared graphically with the damage risk criterion as in Fig. 1. This shows to what extent the noise constitutes a danger to hearing. In the final assessment of the risk, allowance is made for exposure duration if shorter than that quoted. In this way we attempt to assess the risk of deafness for men working in noise.

## The Aeroplane and Aircrews

When one considers the crew in an aircraft, it will be appreciated that they are situated in a noise field of greater or lesser intensity, depending on the type of aircraft, and that

they will be exposed to noise for varying lengths of time, depending on the operational role. For example, jet fighter pilots fly in a relatively quiet environment for short periods, whereas transport and maritime reconnaissance crews fly for considerably longer periods in noisier aircraft. The effects of noise can be divided into short- and long-term effects; the short-term effects are: Interference with communication in flight between members of the crew, or interference with communication over the radio telephone. To this is allied general fatigue, partially induced by noise. Fatigue of the organ of hearing, producing partial hearing loss in flight is by no means uncommon in crews of Shackleton aircraft (Dickson *et al.*, 1953) but, in most cases, the hearing will recover after an adequate rest on the ground. Continued acoustic insult and lack or misuse of protective equipment will perpetuate fatigue into a lasting deafness—the principal long-term effect.

Different measures can be adopted to overcome this, for example:

(*a*) Careful selection of men for aircrew duty. Every effort is made by means of clinical and audiometric testing to ensure that men engaged for aircrew duty have no hearing loss before commencing training, and those with histories suggestive of susceptibility to noise are also excluded. We have not yet been able to devise a practical and easily worked noise-susceptibility test which could be applied to all entries for air or ground service.



FIG. 2.—Cotton flying helmet incorporating the standard R.A.F. earmuff, fitted with telephone receiver.

(*b*) The periodic examination of aircrew, both clinically and by audiometry, is extremely valuable, particularly of those men who show themselves to be susceptible to noise.

(*c*) Examination of the noise itself in the working situation, is of first importance and leads to constructive suggestions both in the shape of protective gear for the men and also such measures as sound insulation of the cabin. This has been done in Shackleton aircraft with a certain amount of success and similar surveys have been done in the Beverley transport aircraft and in the Whirlwind helicopter, where it is hoped that a similar degree of success will be achieved.

(*d*) Further measures may be taken to protect the individual himself, for example, the issue and wearing of a Type F flying helmet, which was devised at the Institute of Aviation Medicine, Farnborough. Laboratory examination of this helmet has shown that it is effective in reducing the noise falling on the ears, and in many cases, may reduce the noise below the level where it may be considered a hazard. Experiments have recently been put in hand in which a radio telephone receiver is incorporated in a protective ear muff, which is, in turn, built into a cotton helmet (Fig. 2). With this device we hope to provide effective

protection for crews of transport aircraft and those employed on maritime reconnaissance. Such a helmet will have the existing advantage of the Type F with regard to clarity of reception on the radio telephone, and will provide effective acoustic insulation. The sound damping of the cabin in selected aircraft has already been mentioned.

In practice, it is convenient, in the light of present-day requirements, to consider the likely hazard for aircrew employed on different operational duties. Pilots of jet fighter aircraft are unlikely to be exposed to hazardous noise, except when taxi-ing before take off and after landing, when the cockpit canopy is generally open. The pilot is protected by a Type F flying helmet, the fit and seal of which is ensured by the addition of a protective "bone-dome" or crash helmet. During flight, he is seated well forward of the engine(s) and is operating in a relatively quiet environment.

The situation with regard to present-day bomber crews is much the same, and it should be noted in passing, that the real hazard from engines powering this type of aircraft is to the ground crew who service them. The hazardous effect of noise made itself felt on crews in piston-engined bombers during World War II, when forerunners of the Type F helmet were devised; while as long ago as 1939 the effect of noise on the ears of aircrew was demonstrated by Dickson and Littler.

In Coastal Command, the noise in the cockpit of the Shackleton aircraft has proved a problem and many field surveys have been done, including pre- and post-flight audiometric testing of aircrews in a mobile hearing test chamber, in order that the degree of hearing loss sustained by the ears on an operational flight could be assessed. The present Mark of Shackleton aircraft now has the cabin insulated and, in addition, a small rest room is provided, which lessens the effects of fatigue considerably. In Transport Command, the engines of the Beverley aircraft produce a high intensity noise field, and many complaints have been received from the crews. Following noise analysis, selected aircraft are being sound-insulated.

### The Aeroplane and the Passengers

At the present time, the aircraft used for trooping are the Beverley and the Hastings aircraft, in both of which the noise level in the passenger compartment is relatively high. In the future, when trooping is undertaken by a Comet aircraft, the noise in the passenger compartment will be negligible. The evacuation of casualties is normally undertaken in Hastings aircraft and the provision of ear defenders should be considered in some circumstances.

### The Aeroplane on the Ground

Today, the power of aircraft engines has increased and it would be opportune at this time to mention the types of aircraft engine which are now in use and to compare the noise emanating from them. The first of these is:

(i) The piston engine, which can produce up to 120 db. s.p.l. overall.
(ii) The turbo-prop with a sound pressure level of 120 to 125 db. s.p.l. overall.
(iii) The turbo-jet engine with a noise output of 125 to 133 db. s.p.l. overall.
(iv) The turbo-jet with after-burner has a noise output of up to 150 db. s.p.l. overall.
(v) Rocket motor (assisting jet take-off) up to 150 db. s.p.l. overall.



Fig. 3.—Ground servicing of a Vampire Fighter showing the positions of the ground crew during engine running.

### The Effect of Noise on Ground Personnel and Its Control

It is the ground personnel who are now most exposed to the noise hazard from engines. Regrettably, many men employed in the aircraft engineering trade group do become very used to working in noisy situations. This is probably due, on the one hand, to familiarity with the working conditions, and also, on the other hand, to the insidious onset of deafness. Where the hazard has been explained to these men, and when efficient and effective protective devices have been shown them, such devices have been received with enthusiasm.

Broadly speaking, ground crew are liable to be exposed to hazardous noise in all phases of the aircraft's movement on the ground, namely taxi-ing, take-off and landing. Those employed on first and second line servicing and also those employed in maintenance units on the servicing of engines, are undoubtedly exposed to hazardous noise (Figs. 3 and 4). For

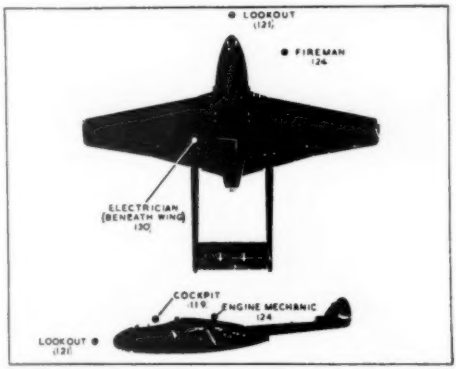



Fig. 4.—A diagram illustrating the position in and around a Vampire aircraft of the ground servicing crew, and the total noise level in their working situation when the engine is running at maximum r.p.m.

those employed on first and second line servicing, the exposure per working day is not, of necessity, great, but, nevertheless, the men need protection; on maintenance units, however, where engines are run on test beds, the hazard is considerably greater and all men working on such sites must be adequately protected.

The problem can be tackled along the following lines:

(*a*) Propaganda disseminated by the Medical Officer and the Senior Technical Officer on the hazardous effects of noise and its consequences. This may also be supplemented by visual instruction and a film is now being made for showing to all ground personnel who are likely to be affected by noise.

(*b*) The periodic check of the hearing of men in exposed situations is necessary, and, allied to this, one must emphasize the desirability of using "individual pure tone" or "group audiometry" before the man starts in employment and at regular intervals during this working life, in order that deterioration in the hearing acuity may be discovered early.

(*c*) Protection for the ears of the individual is an absolute necessity under these circumstances, and, until recently, a small plastic plug was supplied. This was found effective to a certain extent (Dickson *et al.*, 1954*a*), but was not wholly adequate against the damaging effect of high intensity noise from jet engines. As a result, the protective ear muff devised by the National Research Council of Canada was adopted, with certain modifications, and is now in production in this country and being distributed for use by ground crews.

(*d*) The rotation of crews may also be considered, where unprotected or partially protected men are working in very high intensity noise levels for periods which would appear to be hazardous. By this it is quite feasible that, although men would be exposed to high intensity noise, individually they would not be exposed for a period likely to cause permanent damage. This is a technique which may have to be considered for men working on newer forms of propulsive equipment which are now being devised.

(*e*) Mufflers and silencers for engines can be used in an attempt to reduce the noise at source. No wholly effective portable muffler of a type likely to find universal acceptance has been devised as yet and the most effective mufflers are generally those which are static and built in to a muffling pen.

### Effect of Noise on Operations

Noise may have an adverse effect on the conduct of flying operations, principally through interference with communications and the effect of this is likely to be felt in the control tower, the briefing room and some administrative offices. It is our experience that on some airfields the control tower is extremely close to the servicing pans, when the air traffic controllers are exposed, not only to a noise level which makes communication and the reception of verbal signals virtually impossible, but to one which may itself be hazardous to the hearing. It is also within our experience that on some airfields the general administrative offices which control day-to-day life on the station are subject to noise during the time that aircraft are operating from the airfield to an extent that the efficiency of those working in them must suffer. The problem can be tackled on general lines by careful attention to the site and layout of airfields, and to the alteration of the flight pattern, if this is at all possible, in order that affected areas on the airfield may have some relief. Control towers are a problem in themselves and require careful siting and effective sound insulation. The adverse effect of noise on aircrews trying to sleep should not be forgotten.

### Effect of Noise on the Civil Population

It is only on rare occasions that noise falling on a civil population is actually liable to be a hazard to the hearing. The situation of Royal Air Force airfields is such that only relatively small communities are likely to be affected. The annoyance value of noise, however, is one experienced over a relatively wide area surrounding any airfield. It affects particularly those areas related to the servicing pans or to the ends of the runway. Such areas will either have constant annoyance during servicing or, when flying operations are in progress will be intermittently subjected to noise of high intensity, depending on their relation either to the runway or the flight pathway. The problem may be tackled by attempting to reduce the noise at source by the use of silencers, mobile or static mufflers, or by the use of noise muffling pens, and by the alteration of the flight pattern.

Pens have proved of great value at airfields where aircraft are ground tested before flight and delivery. They have the advantage that the noise is contained and the efflux is discharged into a large Cullum muffler. The disadvantage of this equipment is that each type of aircraft requires its own individual pen; for instance, a Hawker-Hunter fighter will not fit into a Gloster-Javelin muffling pen. From the point of view of present operational requirements in the Air Force, it is quite impracticable, therefore, to consider erecting such pens, at heavy cost, when the squadron for whom they are intended might well be moved. It is possible that with the standardization of fighter aircraft equipment during the next few years such an ideal will be realized, when we may have the muffling device for the standard fighter supplied to operational airfields.

The use of deflecting walls has met with only partial success, in that there is no absorption of sound. The noise is deflected, possibly to fall on an area hitherto unaffected. Walls have the further disadvantage with large aircraft that to be effective even locally they must be relatively high.

Probably the most important factor with regard to the alleviation of the annoyance of noise is a good public relations service. This has been well developed in the United States Air Force and every effort is being made within the Royal Air Force on similar lines, whereby responsible persons in civil communities and the community itself are informed of the efforts being made to control the noise; of the difficulty in siting dispersals and in reducing noise at source and of the necessity for maintaining a fully equipped and efficient fighter and bomber force.

It should be mentioned, at this stage, that the muffling of engines in flight is virtually an impossibility. The amount of benefit conferred by such a silencer would be very small in terms of sound reduction, while, at the same time, the efficiency of the engine would be reduced. From an operational point of view this is a technique which cannot be considered; but the noise from aircraft in flight produces problems of its own which can only be tackled by changing the flight pattern and the flight pathways.

### Other Noise Sources

So far we have concentrated entirely on the aircraft engine as being the source of damaging or annoying noise, but mention should also be made of auxiliary equipment used in connexion with aircraft, for example, starter motors and generators. These, particularly if used in an enclosed space, can produce noise levels which would be damaging to the unprotected ear. During repair of aircraft, such procedures as riveting, sand-blasting, metal spraying and vapour blasting may all produce a work situation in which the sound is hazardous and in which the workers require protection.

### The Care of the Deafened

It is pertinent to enquire at this stage into the management of those who have suffered damage to their hearing as a result of exposure to noise. In the first instance they are examined by an otologist to assess the degree of deafness. The individual is then moved away from work in a noisy environment for a period of at least three months. This is followed by re-examination by the otologist to assess the degree of recovery or permanent injury. Where recovery occurs the man is returned to his employment adequately protected, and checked periodically to assess his progress.

When recovery fails to occur the choice lies between re-mustering the man to a trade in which he will not be unduly exposed to noise, or a return to work adequately protected. The latter course is only justified in skilled, highly trained individuals—and must be accompanied by close and regular supervision to detect further deterioration in the hearing. Further hearing loss in such a person will necessitate re-mustering in order to preserve him from severe perceptive deafness, normally associated with persistent and aggravating tinnitus. It must be emphasized that no effort should be spared to save these men from the unhappy lot of irreparable deafness in their later years.

### The Future

The future is shadowed by many problems in this field. With the existing policy pointing to a standard fighter and standard types of bomber, it is possible that development of engines for military use will cease. However, if, as seems more likely, their development continues, to what levels will the noise increase? The use of mobile silencers and mufflers is practically in its infancy and much research is still required to produce an effective muffler for each engine during ground running. Such a mobile muffler will be the answer to many difficulties. The use of rocket missiles introduces many of the problems attendant on the use of artillery, whose role they fulfil. Rocket-powered aircraft will bring similar difficulties in their wake. The use of aircraft employing vertical take-off is still in an experimental stage. Development on these lines is progressing; and while it is possible that the noise initially will be greater, it should be more localized.

Finally, how next do we protect the man? We believe that with the existing ear muff, the Royal Air Force Mark III, we have an adequate defender affording the best degree of protection against existing noise. It is unlikely that any other muff would give more effective protection against greater noise. At first sight, it seems logical to encase the head in a helmet, in an attempt to stop the conduction of high intensity sounds through the bone. The entrance of sound to the body, and its conduction within the body, is a problem which now faces us. On the information which we get from this work, so shall we be able to decide the best means of protecting the individual either by helmet, suit or by an individual cell fitted with remote control. Above all, we must remember the man, who must work while wearing these protective devices.

### Acknowledgments

Before closing, we should recall the work in this field of those who have gone before who have given us a basis on which to approach and tackle the problems created by noise in a modern Air Force.

We wish to thank the Director-General of Medical Services, Royal Air Force, for permission to publish this paper.

### Bibliography

American Standards Association (1954) The Relation of Hearing Loss to Noise Exposure. A report by the Exploratory Sub-committee X-24X-2 of the American Standards Association.

Benox Report (1953) An Exploratory Study of the Biological Effects of Noise. The University of Chicago. Chicago.

Dickson, E. D. D., Ewing, A. W. G., and Littler, T. S. (1947) The Effects of Aeroplane Noise on the Auditory Acuity of Aviators. Contributions to Aviation Otolaryngology pp.1–15. London.

——, Hinchcliffe, R., and Wheeler, L. J. (1953) Investigation into the Hearing Efficiency of the Crews of Shackleton Aircraft. F.P.R.C. 858. Air Ministry, London.

——, ——, —— (1954*a*) Effect on Auditory Fatigue of Sealing and Fitting Tail-Pipe Exhausts to the Shackleton Mk. II. F.P.R.C. 874. Air Ministry, London.

——, ——, —— (1954*b*) Ear Defenders. F.P.R.C. 884. Air Ministry, London.

Gannon, P., and Hinchcliffe, R. (1955) Field Trials of Ear Defenders. Preliminary Report: "Sonex" Ear Plugs. A.L. Report No. 15/55. Air Ministry, London.

Gannon, R. P., and Wentworth-Jessop, J. A. (1956) Noise in Blackburn Beverley Mk. I. A. L. Report No. J.32/11/R.1. Air Ministry, London.

——, —— (1956) Noise in a Sound-proofed Blackburn Beverley Mk. I. A. L. Report No. J. 32/11/R.2. Air Ministry, London.

——, —— (1957) Noise Measurements on a Super Sprite Rocket Motor. A.L. Report No. J. 32/13/R.1. Air Ministry, London.

——, ——, and Jenkin, D. G. (1957) An Ear Defender for the R.A.F. A.L. Report No. J. 3/3/R.1. Air Ministry, London.

HINCHCLIFFE, R., and WHEELER, L. J. (1955) An Investigation into the Effect of Flying on Speech Intelligibility in Noise. F.P.R.C. 917. Air Ministry, London.
KING, P. F., and HINCHCLIFFE, R. (1955) Report on Investigation of Aircraft Control Tower at R.A.F. Luqa. A. L. Report No. 11/55. Air Ministry, London.
KRYTER, K. D. (1950) The Effects of Noise on Man. *J. Speech Dis.* Monogr. No. 1.
PARRACK, H. O. (1951) Physiological and Psychological effects of noise, Proceedings of the Second Annual National Noise Abatement Symposium, Chicago.
ROSENBLITH, W. A., STEVENS, K. N., *et al.* (1953) Handbook of Acoustic Noise Control, Vol. II, Noise and Man. Wright Air Development Center. Technical Report 52–204.
RONGE, H. E. (1955) Hygienic Principles of Community Noise Control. Savlyck ur **IVA, 26,** 3. 354–372.
R.A.F. Acoustics Laboratory (1955) Noise Control; R.A.F. Oakington. A. L. Report No. 7/55. Air Ministry, London.
WENTWORTH-JESSOP, J. A., and GANNON, R. P. (1956) Noise Measurements on the Ground Muffling Pen Mk. II for the Hawker Hunter. A.L. Report No. J. 32/3/R.1. Air Ministry, London.

## DISCUSSION

**Air Vice-Marshal E. D. D. Dickson:** There can be no doubt that noise of the intensity encountered to-day will give rise to hearing loss. The human ear and human nervous system are limited in their tolerance for noise. Having conceded that noise causes hearing loss it is time we considered certain points in evaluating the damage sustained:

(1) Provision of some sort must be made for calculating the percentage disability of hearing that man might have incurred. What sort of test do we give and how do we calculate from that test the percentage of disability? The aim should be to get a number that could be applied to some schedule award for total disability. We must remember that noise-induced hearing loss is not a total loss of hearing function, it is invariably a partial loss.

(2) Diagnosis in determining what kind of hearing the patient has. To this is closely related the problem of causal relation.

(3) The possibility of recovery of function once noise-induced loss has been produced is an important question. Is it permanent? How long do we have to wait to know whether it is permanent or not?

(4) Lastly we must consider the loss which occurs normally—simply as a result of ageing—presbycusis. What is its relation to the hearing loss that may be induced by noise? Does presbycusis make an individual more liable to noise-induced hearing loss or vice versa?

What we must recognize is that noise-induced hearing loss exists and can be related statistically to some factors of noise. These have been stated to include intensity, spectrum and length of time the individual spends in noise. The element of susceptibility has not been sufficiently investigated; it is perhaps opportune to embark on some research project to obtain some clear-cut information.

I want to stress again the importance of pre-employment examination by pure-tone audiometry of all those about to embark on a noisy occupation. But to be of any value it must be carried out under standard and controlled conditions by individuals conversant with the application of the test. Only by periodical surveys will we be able to determine who are the individuals most susceptible to noise—and also the effects of noise in aggravating any pre-existing hearing loss.

In the final assessment of noise-induced hearing loss we must recognize that the ability to hear and understand everyday speech is what we are really interested in when we formulate a percentage figure in hearing loss, and the means for assessing it.

Speech is the thing that is really important about the sense of hearing. We are dealing with the function of receiving speech, the receiving of auditory communication. It is not an anatomical proposition dealing with extremes of hearing either extremely high or extremely low tones or even the very greatest degree of sensitivity, but it is the ability to receive speech. This puts certain limits on the frequency range in which we are interested and means that certain parts of the frequency range are more important than others. If we accept this general principle we at least have a foundation from which we can start in an attempt to assess the disability incurred by exposure to intense noise. We cannot propound a concept of hearing loss due to noise without some means of assessing its effects on social adequacy.

**Surgeon Captain C. N. H. Joynt** enquired whether ear, nose and throat specialists in the Royal Air Force encountered much clinical deafness due to high intensity noise generated by aircraft in the course of their normal practice. He had not encountered many cases over a good many years as an otologist in the Royal Navy and this was also the current experience of ear, nose and throat specialists at Naval Hospitals whose experience on this point had recently been ascertained.

**Wing Commander King,** in reply, said there was no doubt that the time was coming when the disability resulting from deafness would be the subject of a new assessment and that many of the factors mentioned by Air Vice-Marshal Dickson would have to be taken into account.

In reply to Surgeon Captain Joynt's query he said that a full survey was being instituted to obtain further information on this aspect of the problem. It was not the practice in the Royal Air Force to invalid deaf personnel, if this could be avoided, but rather to employ them on other duties where they would not be exposed to further risk of cochlear damage. He pointed out that, on account of the more dramatic onset, a man was much more likely to report deafness resulting from gun-fire than from repeated exposure to the noise of jet aircraft, of which, because of its gradual onset, he might be unaware.

**Spot Diagnosis.** Volume 3. Compiled by the Editors of the *British Journal of Clinical Practice.* (Pp. 140; illustrated; 10s. 6d.) Harvey & Blythe Ltd. 1957.

The art of spotting a diagnosis from a photograph and one or two verbal clues bears as little relation to bedside diagnosis as does the solving of a crossword puzzle to the understanding of an obscure book. All the same it is an entertaining activity and helpful in passing examinations.

This, the third volume of Spot Diagnosis, contains photographs of more than a hundred cases which the reader, or rather the viewer, is asked to solve. The standard of the material is very patchy. Some pictures are quite unfair and I doubt if one in a hundred clinicians could spot the clues in Fig. 6 or the diagnosis in Cases 32, 87 and 88. Case 89—the drawing of a eunuchoid is very poor and a good photograph is needed instead. Yet, on the whole the photographs are well taken and reproduced and the letterpress mainly accurate, and the book will provide diverting snippets of clinical knowledge varying from trivial museum oddities to commonplace clinical essentials.

**Sir George Buckston Browne.** By Jessie Dobson, B.A., M.Sc., and Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., D.Sc., F.R.C.S., F.R.A.C.S., F.A.C.S. (Pp. viii + 143. illustrated. 25s.) Edinburgh and London: E. & S. Livingstone. 1957.

The story of the life of Sir George Buckston Browne is interesting, not only for the success-story it depicts but because it gives an extraordinarily vivid insight into an important transition period in surgical history, that is, between 1875 and 1900. The names of the authors are a guarantee of literary finish, and the publishers have produced the book in delightful fashion. Sir Harry Platt has written a foreword.

Those who are interested in genealogy can feast themselves on chapter one, in which the family-line is traced back to the sixteenth century. (We detected one wrong date on page 2). The main part of the book contains large and well chosen extracts from the autobiography which Sir George began when he was over 90 years of age. Sir Hugh Lett has written an appreciation of Sir George as a surgeon.

George Buckston Browne was the eldest child of Henry Browne, a physician on the staff of the Manchester Royal Infirmary. The father was evangelically-minded, but puritanical views and practices did not appeal to the son who commented "My father and I were the very opposite. We never had a thing or a thought in common". Nevertheless when George wished to seek his fortune in London, his father allowed him £160 a year to study medicine at University College Hospital. He was a successful student, strong-minded, impetuous, independent, business-like, and very ambitious. Thinking he had been unfairly treated in the Final F.R.C.S., he refused to enter again for the examination. He was house-surgeon to Erichsen and qualified in 1874. He became demonstrator of anatomy, and then, suddenly, fortune favoured him. Sir Henry Thompson had noted Browne's ability as house-surgeon, and, being in need of an assistant, asked Browne to work with him. Thompson at that time had the biggest genito-urinary practice in England and probably in Europe. He was accustomed to take three months' holiday in the year and left a great deal of responsible work in the hands of any assistant he could implicitly trust. Browne was very capable and conscientious and, after an initial difficult period of getting used to Thompson's peculiarities, served him faithfully for fourteen years. He became as skilful as, or more skilful than, his master and when, in 1888 he severed his connexion with Thompson he virtually took the premier place in that line of practice in London. Assisted and encouraged by a devoted wife he worked seven days a week for twenty-five years without taking a holiday. He maintained his health by taking long walks in the country around London. Only when he had become wealthy did he begin to take long holidays and to indulge his artistic leanings. Like Thompson, Buckston Browne had strong views on diet, and again like his master he found he was much better in health when he gave up drinking beer, wine and spirits. Curiously enough his example induced his own father to become a teetotaller, so in that at least they had something in common.

After the loss of his wife and only son Buckston Browne used his fortune to benefit worthy causes. The Harveian Society, University College, and particularly the Royal College of Surgeons were the objects of his bountiful generosity. His purchase and endowment of Down House and the establishment of the Buckston Browne Research Farm were among his munificent gifts. In 1926 he was elected a Fellow of the Royal College of Surgeons and in 1931 he was knighted. He died at the age of 94 in 1945. He preserved his faculties to the end and walked long distances when he was over 90. He once visited his fellow nonagenarian in Wimpole Street, Sir Thomas Barlow, and when leaving, his friend wished to call a cab. "No, thank you", said Sir George, "I am only going to Waterloo and shall walk." A wonderful man and a princely donor.

**Coronary Heart Disease, Angina Pectoris, Myocardial Infarction.** By Milton Plotz, M.D., F.A.C.P. (Pp. x + 353; illustrated. 90s.) London: Cassell & Co. Ltd. 1957.

Increased interest in coronary arterial disease in recent years has sprung from increased proficiency in its electrocardiographic diagnosis, and from a wider hope that the cause of atherosclerosis may yield to researches into the metabolism of fats, and that even its prevention may some time be realized. The author of this monograph refuses to accept the disease as the natural outcome of senescence, but impatiently probes the probable part played by multiple factors in its causation, enunciating impartially the opinions of others on this issue, as well as giving his own. This inevitably leads him to discuss controversial matters like the effect of smoking, diet, and anticoagulant or other drugs, on the health of the coronary arteries. All this he has done in a commendable way, for he has written clearly, concisely, and authoritatively on his subject, and has added a comprehensive bibliography to each of his chapters. He deals successively and succinctly with the response of the coronary circulation to disease affecting it or its environment, clinical presentation of coronary arterial disease, its electrocardiographic diagnosis, prognosis, and treatment. The author is emboldened to write on preventive and on surgical treatment, and concludes with a useful chapter on its medico-legal aspects.

No doctor interested in coronary arterial disease—and no doctor can be without this interest—should fail to possess this help to understand it.

**Extensile Exposure.** By Arnold K. Henry, M.B.Dublin, M.Ch.Hon., Trinity College, Dublin and Cairo, F.R.C.S.I., Chevalier de la Légion d'Honneur. 2nd edit. (Pp. xii + 320; illustrated. 45s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

There cannot be a surgeon, certainly an orthopædic surgeon, who is unfamiliar with the first edition of this book in which Professor Henry, in his inimitable style, taught him the first necessity of his craft—to get safely and quickly to bone. The second edition is nearly twice as long. It includes all the material of the first, for the most part unchanged. The new pages are devoted to the extensile exposure of the vertebral artery and the posterior cervical rami, the posterior approach to the stellate ganglion and the left subclavian artery, the anterior approach to upper thoracic ganglia and the pulmonary artery, and the extraperitoneal exposure of the vessels and nerves of the pelvis through a mid-line incision. Also included is an ingenious method of dividing all the sensory nerves of the hip-joint through anterior incisions.

All this material, much of which has been published before in a variety of journals, is presented in the unique style that we have come to expect from one of the world's greatest teachers of surgical anatomy—accurate, vivid and written so attractively as to merit inclusion even in the bedside library. But valuable as it is to have these papers collected under one cover, it is impossible, even though a little churlish, not to regret the demise of the first edition, a gem, unique amongst surgical monographs. The new edition is too much of a hotch-potch of unrelated material to win quite the same place in one's affection.

**Mental Deficiency.** By L. T. Hilliard, M.A., M.B., D.P.M., and Brian H. Kirman, M.D., D.P.M. (Pp. xvi + 517; illustrated. 60s.) London: Churchill. 1957.

This book is largely the work of the staff of the Fountain Hospital, with some assistance from a Medical Research Council team. The hospital cares largely for young low-grade defectives and provides what many would regard as a perfect setting for clinical inertness and a rather drab form of custodial care. How wrong such a concept would be, is very vividly shown in this book. Dr. L. T. Hilliard and his friends have not simply followed the design and text of other books, but have set out boldly to describe in their own way the social, pathological and clinical aspects of mental deficiency. They have not hesitated to attack—for example in the section on cretinism—things which in their own extensive experience, they believe to be misconceptions. They have also described in a most readable way details of the law as it applies to defectives, and the social arrangements made for them outside hospitals.

The result is a textbook which is clear and comprehensive, and is probably well ahead of anything now available in English. It is beautifully produced and well illustrated. The two principal authors have left the writing of the pathology section to a neuropathologist, Dr. L. Chrome; and the psychology section has been written by Dr. J. Tizard and Dr. N. O'Connor. The separation of pathology and clinical accounts is sometimes mildly inconvenient perhaps, but cross references are plentiful and the index is full. The book deserves a wide circulation among doctors, medical students, and lay workers in mental deficiency.

[*Continued on p.* 55

**The Physiology of Nerve Cells.** By John Carew Eccles. (Pp. xii + 270; illustrated. $5.75.) Baltimore: The Johns Hopkins Press. Distributed in Great Britain by the Oxford University Press. 1957.

The investigation and analysis of the electrical activity of the nervous system has been dependent upon accurate methods of magnification and recording of minute changes of electrical potentials lasting for periods as brief as 0·1 m.sec. The application to these problems in the last twenty-five years of thermionic valve amplifiers and cathode-ray oscillographs opened up a wide field for research, of which full advantage has been taken. In the last five years or so, the need to narrow down the observations to the changes occurring in a single neuron has been made possible by the micro-electrode. The cell with its axon and dendrites and its surrounding multitude of synaptic knobs remains in situ, while its individual activities can be recorded as though it were isolated. The tip of a micro-electrode has a diameter of from 0·5 $\mu$ to 1·0 $\mu$, and by a micro-manipulator it can be passed through the wall of the cell so as to rest within its substance. Penetration of the cell is recognized by the special characteristics of its electrical record. Complementary to this technique has been the histological study of the cell and the synaptic knobs with the electron microscope. The great magnification has made possible measurements of the size of the knobs, and of the synaptic clefts which separate them from the cell-membrane; such measurements have been valuable in the understanding of the physics of synaptic transmission and have corroborated conclusions drawn from the studies of electrical activity at this site.

In this engrossing book, Professor Eccles has gathered together the observations of his own department of research, and those of others in this field. He has improved the micro-electrode still further, by making it twin-barrelled. By this means the cell can be subjected to a change of its resting potential, or to a variation of its ionic composition, and the effects on its electrical characteristics recorded during the passage of nervous impulses. A wide variety of experiment and of careful measurement has resulted in the definition of the electrical properties of the cell membrane, of synaptic activity and of the cell discharge which is propagated down the axon as an impulse. For the first time, it has been possible to demonstrate graphically, and to explain satisfactorily in electrical terms, the process of inhibition of the discharge of a cell by synaptic activity, Much is now known of the physical characteristics of synaptic transmitter substances, but the identification of these substances within the C.N.S. has failed, with one exception. Acetylcholine has been shown to be responsible at the synapse for exciting the Renshaw cells (situated in the ventro-medial part of the anterior horn of the spinal cord) which exert an inhibitory action on the motoneurones of the same segment. In the last part of his book, Professor Eccles comments on "aspects of functional architecture of the C.N.S." He suggests that there are basically two types of nerve-cells, excitatory and inhibitory All inhibitory action has been observed so far to be exerted by short-axon interneurones only, and he postulates that long pathways are formed by axons of excitatory cells, and inhibitory cells are short-axon neurones lying in grey matter. In the serial links of neuronal pathways, the question is asked whether there is a regular alternation in the nature of the transmitter substance employed. Although the latency of action of all synapses is about the same, the duration of the synaptic activity varies considerably; this could be explained if a barrier existed around certain synaptic clefts, preventing the diffusion of the transmitter substance.

The information brought together in this book is concentrated, and the reviewer found it necessary to revise his scanty knowledge of physics in order to appreciate the elegance of the experiments and the significance of the findings. But the effort is well worth while, in order to keep abreast of this fascinating field of work. Such fundamental knowledge concerning the units of the C.N.S. will ultimately have far-reaching effects, both in the understanding of disorders of neural function and in treatment.

**Principles of Epidemiology.** By Ian Taylor, M.D., M.R.C.P., D.P.H., and John Knowelden, M.D., D.P.H. (Pp. vii + 300; illustrated. 30s.) London: J. & A. Churchill Ltd. 1957.

A book on the principles of epidemiology is welcome as it is over twenty-five years since publication of the last comparable work on the subject. Students and practitioners of public health and preventive medicine, and the increasing number of others who now find it useful to employ epidemiological methods in their inquiries, will study it with interest. They will find a book with many virtues, though some may be disappointed that the emphasis is so heavily upon infectious disease.

The first four chapters are devoted to sources of epidemiological information and to a

fairly detailed description of simple statistical methods used in its analysis. Assessment of results is discussed briefly but no reference is made to the use or abuse of tests of significance. Subsequent sections deal with agents of infection, modes of transmission and the consideration of those characteristics of man and his environment which influence the pattern of disease in the community. The problem of how much statistics and microbiology to include in a book of this kind is a difficult one that the authors have resolved reasonably well; only those aspects of these subjects that are essential to the study of epidemiology have been included. No attempt is made to describe the epidemiology of individual diseases but principles are abundantly illustrated by practical examples, mostly of topical interest. References, given as footnotes, are well chosen and just sufficient in number to allow the more important arguments to be studied further. Considerable care has been taken over the accuracy of information that is presented and there is little evidence of personal bias in the discussion of controversial matters.

This book should prove a useful introduction to the principles of epidemiology for students of public health and public health bacteriology. It is a sound guide to established practice and though not stimulating, is clear, concise and easily read. It will probably be found less useful by those who seek guidance on the application of epidemiological methods to new problems. The authors acknowledge in their preface that these methods are now being used more widely but the fact that they have chosen to take their examples from, and centre discussion round, infectious diseases will not help the student to understand the way in which lessons learned from the study of measles can be applied, for example, to mental disease.

**Collected Papers of the Mayo Clinic and the Mayo Foundation.** Vol. 48. 1956. (Pp. viii + 788; illustrated. 87s. 6d.) Philadelphia and London: W. B. Saunders Co. 1957.

The policy behind the production of these annual volumes of papers from the Mayo Clinic is such that the reader does not necessarily expect a complete tracing of the tenuous and irregular growing edge of surgery, but rather evidence that surgical procedures have become established. He will thus not be surprised that there is no mention of the position of hormonal surgery in cancer, and he will probably rightly conclude from its omission that the subject has not yet developed to the stage at which it can be sold as a guaranteed article to the shrewd and critical American public. The volumes must be judged therefore by what they do contain and not by what they do not pretend to contain, and the reviewer has an embarrassment of riches in his choice of what to note.

In the cardiac surgery section, two of the most striking articles are on surgical correction of ventricular septal defects which has been done in 36 cases, and on resection and grafting for aneurysm and thrombotic occlusion of the abdominal aorta. The latter operation has been performed in 59 cases with 7 deaths for aneurysm, and in 47 cases with 2 deaths for thrombotic occlusion. In the alimentary tract section, there are six articles on benign tumours of the liver, but formal hemi-hepatectomy with preliminary vascular control does not seem to have been attempted. Four articles on resection of the colon for diverticulitis reflect the increasing frequency of this procedure.

In the section on the ductless glands, it is interesting to note that carcinoma was the cause of 46 out of 130 nodular lesions of the thyroid gland in children, and that injury of the recurrent laryngeal nerve during thyroidectomy seems equally common (or, more strictly, uncommon) in the practice of both the surgeons that do and those that do not expose the recurrent laryngeal nerves as a routine.

In the head, trunk, and extremities section one notes that hemipelvectomy is now regarded as a routine standard procedure, 50 cases of malignant tumour having been treated in this way. The development of parotidectomy for parotid tumours has been surprisingly slow at the Mayo Clinic, especially bearing in mind the pioneer work at the Clinic of Sistrunk, and of Adson and Ott. The article by Judd calling for a "much more thorough surgical approach than was used formerly" is therefore an interesting pointer. The article on operative cholangiography in the radiology section also shows a change of attitude. Previously, the surgeons of the Mayo Clinic have seemed rather hostile to this procedure, on the grounds that it is hardly worth the time it may necessitate, and that it is often misleading. The excellent article by Ferris and Weber is, however, very favourable to operative cholangiography. Perhaps the key to the change of attitude is provided by the sentence emphasizing that the success of the test depends on attention to detail, and on the close co-operation of the radiologist with the surgeon and anæsthetist.

# Section of Otology

President—I. SIMSON HALL, F.R.C.P.Ed., F.R.C.S.Ed.

[*November* 1, 1957]

## Otosclerosis, a Twenty-year Retrospect

### PRESIDENT'S ADDRESS

By I. SIMSON HALL, F.R.C.P.Ed., F.R.C.S.Ed.
*Edinburgh*

IN the middle nineteen-twenties the fenestration operation was not unknown in Edinburgh and my predecessor, Dr. John S. Fraser, had already done some of these operations, but abandoned the method on account of its dangers, as did Jenkins in London, and Bárány in Sweden.

My interest in the surgery of otosclerosis was aroused by the Address which Professor Maurice Sourdille, then of Nantes, gave to this Section in May 1930 (*Proceedings*, **23**, 1443). Since the common attitude to otosclerosis was entirely defeatist the work described by Professor Sourdille could not fail to arouse interest and curiosity.

At this period the dangers of the operation were of paramount consideration, and it was considered by many to be unjustifiable. This outlook dictated the method, and was the reason for the multi-stage operation practised by Professor Maurice Sourdille, and indeed continued to this day by some outstanding surgeons on the Continent.

Throughout this time Professor Holmgren's name was one to conjure with otologically, and a visit to Stockholm in 1938 provided many ideas particularly regarding the use of the operating microscope.

It was not until the introduction of chemotherapy that we could safely undertake the single-stage procedure as was demonstrated in the first instance by Julius Lempert. It is perfectly true that at the present time I do not use routine antibiotics at fenestration, but the knowledge that they are available if needed gives confidence and peace of mind. My earliest successful case which still retains the original improvement in hearing was commenced in 1936 and completed in 1937.

#### PATHOLOGY

In the course of work such as this it is inevitable that interests other than those in the merely technical aspects of the subject are aroused. Interest in the pathology of this condition one might say is traditional in Edinburgh. J. S. Fraser was one of the keenest students of diseases of the temporal bone in this country, and I am glad to claim friendship with Professor Felix Nager of Zurich, for to study in his laboratory I owe a great deal of the early stimulus to investigate the pathological background of otosclerosis.

The theories of the origin of otosclerosis fall roughly into three groups. We have the vascular theory originally suggested by Wittmaack, and more recently brought up to date by Dorothy Wolff. There is the group of theories of absorption by lacunar erosion and progress of the disease along the blue mantle; this was held fairly strongly by Professor Nager. And finally we have those theories which rest upon the embryological remnants which are found in the temporal bone.

Practically all these theories assume a disease entity. Some have suggested that there might be some underlying condition which predisposed to the onset of the disease. I started myself from this standard position that there was a disease and that it was necessary to discover the cause, to study its course and to follow it through the various stages.

After examining a very large number of sections I was struck by the fact that there was no evidence of spreading disease. In fact I could discover nothing but the signs of healing of bone. This seemed to me the more remarkable because the material I was examining was not post-mortem material from patients chiefly in the later age groups, but was bone taken from young people with, in many cases, a short history of deafness and a progressing disability.

If one was able therefore to discover nothing but signs of bone reconstruction, the conclusion seemed to be inescapable that there had been an acute condition present at some time

during the past. This was borne out to some extent by the presence in one or two cases of osteoclasts—but these were for the most part degenerated. As the condition which brought the patient to operation was increasing deafness, healing and increase of deafness seemed inseparable, and re-orientation of ideas seemed necessary here, and because one had been conditioned to accept otosclerosis as a disease entity, it was some time before I could bring my mind to accept the possibility that in fact we were dealing with a healing process in bone and not with a disease at all. Instead of trying to explain the changes of otosclerosis by new or unusual types of bone process, it seemed to me that if otosclerosis could be explained within the commonly accepted ideas of bone pathology we were more likely to approach the core of the problem.

Two questions therefore appeared to require an answer in this conception of the pathology of otosclerosis. First of all what was the condition of the bone originally, which predisposed it to this particular change. Secondly, what was the condition which triggered the healing process?

To begin with there is a sudden, probably inflammatory, condition of the bone in which osteoclasis plays a large part. There is sharp reaction in the bone which is evident from the production of hyperostosis. I have been able to show that hyperostosis is not the result of prolonged inflammation but is one of the earliest changes in otosclerotic bone and is probably dependent upon the activity of the first stage of the condition. Why, therefore, should the bone in a particular part of the labyrinth capsule undergo this change? I believe that in some of the other conditions affecting the temporal bone we may find some assistance in understanding this particular process. For instance, Paget's disease has been called a localized form of otosclerosis. Fragilitas ossium has many characteristics in common with otosclerosis, in that it has been stated that between 40% and 60% of all cases of fragilitas ossium suffer from otosclerosis. It is noteworthy also that in fragilitas ossium the onset of deafness occurs with the healing of the bone, suggesting again that healing of bone and deafness are concurrent.

It is also noteworthy that in these diseases healed bone is characterized by the production of a mosaic pattern; this can be demonstrated in otosclerosis, in Paget's disease, and in fragilitas ossium where otosclerosis has occurred. And if indeed in fragilitas ossium 40%–60% of all cases have demonstrable otosclerosis in the labyrinth capsule, it might be reasonable to believe that the production of the mosaic pattern which we interpret as otosclerosis is, in fact, evidence of the healing of the bone. If this should be so, then otosclerosis itself, particularly in the production of a mosaic pattern such as it produces, is again merely an instance of healing bone. And this will take us still farther back to the idea that there is a fundamental embryological abnormality of the bone similar perhaps to the lack of osteoblastic tissue which is found in fragilitas ossium, which in its healing after the influence, let us say, of inflammation or other agent, produces what we call otosclerosis. In fact the two diseases may be identical.

## Anæsthesia

In the earliest stages local anæsthesia was the anæsthetic of choice, and for the first 50 patients or so I used nothing else. I found, however, that in the main, our patients were not suited to local anæsthesia and some substitute was sought. I tried basal anæsthetics commencing with oil-ether, and Avertin, and I think I have experimented with every known sequence of inhalation anæsthesia.

At present our method is that induction is carried out with thiopentone, with or without a relaxant, and following intubation, gas-oxygen is the chief agent with the addition of trilene or other inhalant gas, as considered necessary. Blood pressure is reduced to between 60 and 80 mm.Hg. Unless it is lowered to 80 mm. we rarely find there is much advantage and 80 mm. therefore is our threshold.

The use of induced hypotension in an operation of this character is a calculated risk, and it is essential that such a risk should be justifiable. Examination of results in the various groups of cases will show that the risk is justifiable.

## Training

In the selection of patients for this operation there is no substitute for careful study of one's own patients. A certain amount can be learnt from the accounts of others, but some volume of work is essential if even reasonable results are to be achieved.

I believe that in otology there is no place for the occasional fenestrator. The young man who wishes to carry out this work and achieve a measure of success must be prepared to do much hard practice which can only be obtained in the first instance upon the cadaver. I would advise those coming to cadaver work for the first time, that it is of little use to drill a few casual holes in temporal bones. I believe that it is essential that the whole fenestration apparatus should be brought into play on every occasion; this is our method in Edinburgh.

### Classification of Patients

I have taken for analysis a thousand consecutive operations. Before considering these in detail, some definition of terms is necessary. We have to know what constitutes a successful operation. We must decide whether the social adequacy index is necessary for success, and we also have to know into what groups or classes we propose to divide our patients.

I do not consider achievement of social adequacy necessary for success. That is to say I would not reject a patient for operation because I did not feel that he would reach the social adequacy line. There is no doubt that a very high percentage of successful results can be obtained if a surgeon confines himself to patients likely to reach social adequacy, but success or failure should rest I think on far wider and more practical grounds than these. Two requirements must be fulfilled in every case. The audiogram must show a significant rise, above any possible daily variation, and the patient must be convinced that real benefit has resulted from the operation.

### Grouping of Patients

For my own study, I divide my patients into the usual three groups; class 1, the ideal case; class 2, offering not quite such a high probability of success; and class 3, where the probability of success is low. I also have a group 4, which was experimental, into which no cases have gone for a long time, but which was a necessary group in the earlier stages of the operation when we had no data as to what we could or could not do with fenestration.

I feel that if a surgeon accepts a patient for operation then that patient, irrespective of what class he or she is in, is included in any statement of results. The point of studying various classes of patients is not for the patient's benefit but for the surgeon's. Because upon his experience of what is possible within each class the surgeon bases the knowledge upon which he explains to the patient what chances that individual will have of successful operation.

I have divided the patients into groups on a time basis, showing the various types of operation which have been employed. The groups are few, because only one major change in method has been made at a time, and it took me about two years to obtain statistically valid series. Another two years had to elapse before that group could be assessed properly.

The various groups are shown in Table I.

The results in each group are shown in Tables II–V.

It is interesting to study the results on a long-term basis, and the results in all cases operated upon between 1942 and 1947 are shown in Table VI. Some later deterioration can be expected and its extent is shown here.

Table I.—Grouping of 1,005 Cases

| | | |
|---|---|---|
| Improved technique | 1943 | 78 |
| Cartilage implant | 1945 | 189 |
| Contact technique | 1947 | 298 |
| Contact technique (with B.P. control) | 1950 | 440 |

Table II.—Improved Technique

| | |
|---|---|
| Total cases .. | 78 |
| Not traced .. | 15 |
| Cases under review | 63 |
| Successful .. | 45—71% |
| Failed .. .. | 18 |

Table III.—Cartilage Implant Group

| | |
|---|---|
| Total cases .. | 189 |
| Not traced .. | 27 |
| Cases under review | 162 |
| Successful .. | 106—65% |
| Failed .. | 56—35% |

Table IV.—Contact Group

| | |
|---|---|
| Operations performed | 298 |
| Cases not traced | 27 |
| Cases under review | 271 |
| Successful .. | 223—82% |
| Failed .. | 48—18% |

Table V.—Group with Controlled Hypotension

| | |
|---|---|
| Total cases .. | 440 |
| Available for study | 396 |
| Not traced .. | 140 |
| Cases under review | 256 |
| Improved .. | 230—90% |
| Failed .. .. | 26 |

Table VII.—Revisions

| | |
|---|---|
| Total .. .. | 59 |
| Not traced .. | 14 |
| Under review .. | 45 |
| Successful .. | 32—71% |
| Failed .. .. | 13 |

*Revisions* done between 1943–7

| | |
|---|---|
| Total .. .. | 21 |
| Successful .. | 16—76% |
| Failed .. .. | 5 |

Table VI.—Results after Ten Years 1942–1947

| | |
|---|---|
| Immediate improvement .. .. .. | 82% |
| Two-year improvement .. .. .. | 78% |
| Improvement maintained for ten years .. | 74% |

### Summary of Results

| | Number in group | Not traced | Under review | Failed | Successful |
|---|---|---|---|---|---|
| Improved technique .. | 78 | 15 | 63 | 18 | 45 (71%) |
| Cartilage implant .. .. | 189 | 27 | 162 | 56 (35%) | 106 (65%) |
| Contact .. .. .. | 298 | 27 | 271 | 48 (18%) | 223 (82%) |
| Controlled hypotension .. | 440 | 140 | 256 | 26 | 230 (90%) |

### Operative Technique

[The details of operative technique were shown in the film with which the President concluded this Address.]

In the first instance I followed Professor Sourdille's second technique closely (Sourdille, 1930). His operation resembles the operation as we know it to-day. It is a matter of personal chagrin to me in that this is the technique which I originally used and yet, following personal communication with Professor Sourdille, I abandoned it and adopted his first method wherein the incus was left in place, until it became evident that there was no advantage in making difficulties where difficulties need not exist.

My own technique is, I believe, the simplest technique which I have ever practised. I have used both post-auricular and endaural incision, but have always believed and taught that the method of soft tissue approach has nothing to do with the operation itself; the whole crux of the matter rests on making a satisfactory opening into the labyrinth in such a way that that opening will remain patent. The present method of cutting the opening in the canal is something which was developed in Edinburgh and owes nothing to anybody so far as I am aware.

The after-treatment of these operations is of considerable importance, because it may shorten or lengthen convalescence very greatly. In general my habit is to graft the cavity with a Thiersch graft, spread preferably upon linen. This method of cavity treatment has been criticized, but this method of skin grafting was based upon the results in a series of 500 mastoid operations (Hall, 1942), in which healing following skin grafting was clearly superior in my hands to healing by granulation and epithelialization. One relies upon one's own experience if it is sufficiently extensive.

My success, or rather lack of it, is very clearly seen because 13% represents the proportion of my patients who still have a discharging cavity. Unfortunately it is greater than that I had in the series of 500 mastoid cavities before we had the aid of chemotherapy. Why these clean cases should give so much trouble is one of the mysteries yet unsolved.

In my experience discharge takes two forms, one is the infected posterior cell, and the other is the leak which comes over the top edge of the attic portion of the tympanomeatal flap. The second type I find comparatively easy to cure with trichloracetic acid and a little patience, but the infected cell is more difficult because further operation may be required before it can be completely cleared up. Unfortunately the majority of these cases occur in patients in whom the cell system is large and extensive. There is no guarantee therefore that having cleared out the cells once, other and further cells will not repeat the process. This experience has induced a conservative attitude towards re-operation.

In order to shorten the period during which the patients suffer from disabilities of balance exercises are given to the patients after the method of Terence Cawthorne and F. S. Cooksey, and a class is run by the physiotherapy department.

There is no doubt in my mind that the fenestration operation produces a life-long disability in some patients and potentially in all. Patients require continuous attention at intervals which certainly increase until once every year or once in two years is sufficient, but still in the early stages supervision is essential, if the best results are to be obtained. Further, there are certain occupations or amusements which are barred for good to the patient; bathing is always a potential source of danger, and surfing and diving are absolutely forbidden. It is these disabilities which induced many workers from Professor Holmgren onwards, to experiment with other types of fenestration, including the closed fenestration, which did not involve the production of a large vulnerable cavity in the mastoid.

There is no doubt that a good result can be obtained with this particular form of operation. The chief problem here which has occupied many people's minds is to decide what type of material should be used to cover the fenestra. Professor Holmgren tried many types and the one with which he was experimenting most recently was the mucoperiosteum which normally lines and covers the ampullary part of the horizontal semicircular canal. Garson has used conjunctiva. Suggit has used skin, and I also have used a Thiersch graft. There is no doubt that if the same proportion of lasting improvement could be obtained as with the open fenestration, then this operation would receive a new lease of life and much greater popularity. I feel that there is a place for this type of operation, especially where climatic and other conditions render the care of a cavity difficult or impossible.

### Mobilization

There is not time to include the operation of stapes mobilization, but I wish to bring that operation into focus. I believe that this operation has come to stay. It has very definite usefulness and its scope and application are wider than those of the fenestration operation

could ever be. I do not now perform the fenestration operation until the effects of mobilization are known and have been tried. I consider that the one operation is complementary to the other.

### Revision Operation

The revision operation is an integral part of the fenestration procedure and anyone considering himself a complete surgeon in this respect ought to be prepared at any time to undertake it. I have carried out 59 revisions with the results shown in Table VII.

One of the most interesting groups is those with cartilage implant. In this group results were outstandingly good, and if all the failures could have been revised a very high final percentage of success could have been obtained.

The revision operation has been characterized as unjustifiable because of its dangers. With that opinion, of course, I could not possibly agree, and I would like to remind you of a saying of Professor Sourdille's that: "One should always in the making of a fenestra leave room for the revision." The reason for this is that when closure takes place it is frequently from the rear, i.e. from the canal forward over the ampulla, and the easiest place to start a revision is anterior of the ampulla working back towards the old opening. Sourdille's dictum has a great deal of meaning when one considers it from that aspect.

It was in studying revision cases that I came to the conclusion that one of the chief sources of failure was the accumulation of serum underneath the flap. It was for this reason that I proceeded to develop what I have called the "Contact" method of fenestration, whereby the space between the tympano-meatal flap and the membranous canal is minimal. The ideal I believe is that the membranous canal should lie just at the level of the bony wall on either side.

### Bilateral Operations

Altogether 8% of my patients have had operations upon both ears. It is quite obvious that when the second ear is operated upon successfully the effect upon the patient is not nearly so dramatic as in the case of the first operation. Apart from giving the patient a certain amount of balance in hearing and facility at the dinner table or board meeting, there seemed to be little real value, except as an insurance in case anything should go wrong with the first ear. I examined this problem using a speech audiometer in a free field. The speech audiograms make it clear that there is a very real gain in binaural hearing after operating upon the second ear.

There are quite clearly certain disadvantages in the operation, because I have found that troublesome vertigo is very much more likely after the second operation than after the first. For this reason I have always paid considerable attention to the patient's habits and occupation before consenting to operate upon the second ear.

### Changing Technique

I believe it is true to say that no six months have ever passed without alteration in some point of technique, and I would hope that our present results will help in further improvements in the future.

### REFERENCES

Hall, I. S. (1942) *Edinb. med. J.*, **49**, 352.
Sourdille, M. (1930) *Proc. R. Soc. Med.*, **23**, 1443.

[*December* 6, 1957]

A discussion on **Stapes Mobilization** was opened by Dr. Samuel Rosen (New York) with a paper entitled **Stapes Surgery for Otosclerotic Deafness**; other opening papers were read by Mr. Terence Cawthorne and Mr. R. S. Venters.

Mr. A. Finlay Brown, Mr. S. W. Allinson, Mr. H. D. Brown Kelly, Mr. William McKenzie and Mr. I. A. Tumarkin took part in the subsequent discussion.

The meeting will be published in the *Journal of Laryngology*.

## BOOKS RECEIVED FOR REVIEW

**Baron (D. N.).** Essentials of chemical pathology. pp. xii + 247. London: English Universities Press. 25s. 0d. 1957.

**British National Formulary 1957.** Alternative Edition. pp. 245. London: Pharmaceutical Press. 7s. 6d. 1957.

**Campbell (E. J. Moran).** The respiratory muscles and the mechanics of breathing. pp. xvi + 131. London: Lloyd-Luke. 20s. 0d. 1958.

**Commission on Chronic Illness.** Chronic illness in the United States. Vol. 1. Prevention of chronic illness. pp. xxii + 338. Harvard University Press. London: Oxford University Press. 48s. 0d. 1957.

**Cope (Sir V. Zachary).** The early diagnosis of the acute abdomen. 11th edit. pp. 188. London: Oxford University Press. 18s. 0d. 1957.

**Flavell (G.).** An introduction to chest surgery. pp. 354. London: Oxford University Press. 30s. 0d. 1957.

**Gainsford (W.), and Lightwood (R.), eds.** Pædiatrics for the practitioner. Supplement 1957. pp. v + 157 + 8. London: Butterworth. 35s. 0d. Combined price £14 10s. 0d. 1957.

**Gillis (L.).** Artificial limbs. pp. xiv + 449. London: Pitman. £15. 1957.

**Glyn (J. H.).** Cortisone therapy: mainly applied to the rheumatic diseases. pp. x + 162. London: Heinemann. 21s. 0d. 1957.

**Loraine (J. A.).** The clinical application of hormone assay. pp. xii + 368. Edinburgh and London: Livingstone. 30s. 0d. 1958.

**McIlwain (H.).** Chemotherapy and the central nervous system. pp. viii + 328. London: Churchill. 45s. 0d. 1957.

**Palmer (E. D.).** Clinical gastroenterology. pp. vii + 630. London: Cassell. £6 17s. 6d. 1957.

**Proctor (D. F.).** Anesthesia and otolaryngology. pp. xv + 267. London: Baillière. 56s. 0d. 1957.

**Rob (C.), and Smith (R.).** Operative surgery. Vol. 5. Orthopædic surgery. pp. xiii + 366 + 5. London: Butterworth. £5 10s. 0d. 1957.

**Short (C. L.), *et al.*** Rheumatoid arthritis. A definition of the disease and a clinical description based on a numerical study of 293 patients and controls. pp. x + 480. Harvard University Press. London: Oxford University Press. 55s. 0d. 1957.

**Tonkin (R. D.).** The story of the peptic ulcer. Characterised by R. K. Hellier. pp. 71. Philadelphia and London: Saunders. 16s. 0d. 1957.

## BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

**Bakhsh (I.).** Modern medical treatment. 2 vols. Lahore: Panjab University Press. £6 10s. 0d. 1956.

**Brooks (E. St.J.).** Sir Hans Sloane: the great collector and his circle. pp. 234. London: Batchworth. 1954.

**Buerger (M.).** Altern und Krankheit: Grundlagen einer biorheutischen Nosologie. 3rd edit. pp. 684. Leipzig: Thieme. DM 45. 1957.

**Cemach (A. I.).** Diagnostik innerer Krankheiten in Tabellenform. 8th edit. pp. 58 (folding tables). Munich: Lehmann. DM 29.80. 1957.

**Cohen (R. A.).** Short-title catalogue of works on dentistry and allied subjects in the library of R. A. Cohen. Typescript. 1957.

**Cope (Sir V. Zachary).** The early diagnosis of the acute abdomen. 11th edit. pp. 188. London: Oxford University Press. 1957.

**Current Therapy.** Latest approved methods of treatment for the practising physician. Ed. by H. F. Conn. 8th series, 1956. pp. 632. Philadelphia and London: Saunders. 77s. 0d. 1956.

# United Services Section

President—Sir CECIL WAKELEY, Bt., K.B.E., C.B., F.R.C.S.

[*December* 5, 1957]

## Submarine Medicine on U.S.S. Nautilus and U.S.S. Seawolf

By Lieutenant Commander JOHN H. EBERSOLE

*Medical Corps, United States Navy*

### INTRODUCTION

IN the past few years the highly specialized field of submarine medicine and submarine physiology has been deeply involved in the revolutionary changes brought about by the advent of the nuclear submarines, "Nautilus" and "Seawolf". To-day there is more than promise that the problems of nuclear power will involve all fields of military medicine and this is not limited to military medicine alone, for the application of nuclear energy for civilian power, already in being in the United Kingdom, promises to bring these problems to civilian medical practitioners, particularly in the field of industrial medicine. While some of the problems met on "Nautilus" and "Seawolf" are limited to submarines because of their unique operational environment, many others apply equally to all reactor installations, either military or civilian, sea-going or shore-based. The experiences that submarine medicine has had in these initial years may, therefore, be justifiably utilized for a realization of the part that medicine will play in the nuclear age.

There are three important areas in which nuclear propulsion has strikingly added scope and depth to the field of submarine medicine. The first of these is a result of the new environmental situation created by reactor propulsion—an environment which bears little similarity to that of the conventional submarine. While understandable, it is erroneous to think of the medical problems of nuclear submarines as being a simple continuum of previous submarine problems to which has been added the factor of nuclear radiation. The environment of the true submersible, its effects and its control under prolonged submergence, represent a really new and unique entity, and radiation is but one of many factors.

The second significant change in submarine medical practice aboard a nuclear submarine lies in the necessity for strict supervision of radiation control measures during in-port periods. For the most part medical and toxicological problems of previous submarines have been minimal during in-port periods of maintenance. In contrast, in nuclear submarines, radiation control measures have actually greater significance during such periods than while at sea. It is during this time that reactor shield integrity may be broken in order to allow workmen access to the reactor system and to allow work on contaminated components in areas of radiation flux. Medical personnel must therefore be on the *qui vive* during any such period until the operation is completed in order to control exposure and to insure against spread of contamination. In quantitative terms, if alertness may be so quantitated, approximately four times more attention is required, based on relative exposure during maintenance as compared to that at sea.

The third, and perhaps most important, factor that has expanded the boundaries of submarine medicine is that on nuclear submarines a medical officer is directly assigned as a crew member, and is on board for all operations. Evaluation of the medical problems, therefore, no longer depends upon short term on-board observations in a guest capacity. The full impact of this intimacy is only beginning to be realized, but it can be assumed certainly that definition of the manifold problems cannot help but be improved. The rapid "break-throughs" in nuclear technology and the acceleration of new developments demand such intimacy for optimum results and maximum benefit to the submariner, whose health and efficiency are the prime interest of submarine medicine. This opportunity for daily, intimate, and long-term contact with the submarine and its problems may perhaps be ranked as the most important development in submarine medicine since its inception.

While this paper deals primarily with the radiation problem on nuclear submarines, it is necessary in introduction to re-emphasize the point that nuclear power represents more than just a radiation problem to submarine medicine. It is basically a study of the effect of a novel environment on the human organism.

### THE SUBMARINE ENVIRONMENT

It has been stated previously that the nuclear submarine environment is unique; it is necessary, however, to reiterate this point, for it profoundly affects radiation control technique and, indeed, provides a leitmotiv in the formulation of the radiation hygiene programme.

The single most important factor in the environment with which we deal on nuclear submarines is the capability for long submergence independent of the Earth's atmosphere. All previous submarines have been dependent upon air, save for relatively short periods, rarely exceeding twelve hours, at which time contact with the Earth's atmosphere was re-established. Once on the surface fresh air was circulated in the ship to dilute and displace toxic atmospheric elements accumulated in the ship during its submerged period.

Surfacing of the submarine at that time was required to run diesel engines, which, in turn,

charged the electric storage batteries which propelled the ship when submerged. Operation of such diesel engines is an aerobic process—the combustion of oxygen and a fossil fuel.

The diesel snorkel has not significantly changed this situation for the snorkel tube, carrying air to the submerged submarine for her diesels, also carried fresh air to the ventilation system and to the crew as a secondary effect. Snorkelling must, therefore, be considered as a simple variant of full surface operations in which communication with the open atmosphere is maintained although the ship is submerged.

The impact of nuclear power lies in the fact that splitting or fission of the uranium atom to furnish heat for the production of steam is an anaerobic process—indeed, for technical reasons, oxygen must be excluded from the process. Given this as the basis for a propulsion system, rather than oxygen-dependent diesels, true submersible capability is achieved.

Visualize such a true submersible as a streamlined capsule operating beneath the ocean's surface. This microcosm, this sub-miniature world, must maintain an independent atmosphere and an ecology compatible not only with life, but with efficient combat life for the the personnel contained within it. A most important limiting factor in this ecology is that such an atmospheric volume is contained and finite; therefore, little atmospheric dilution of any toxic air-borne substance can be expected. We will see later how this relates particularly to the control of air-borne radioactive contamination.

In such an environment three basic conditions must be met in order to support life:

(*a*) Continuous supply of oxygen to maintain normal atmospheric concentrations.

(*b*) Continuous removal of normal human metabolic products, i.e. carbon dioxide.

(*c*) Prevention of or provision for removal of any toxic substance released by ship's equipment.

As a corollary to these a vigorous and continuing study must be made of atmospheric conditions aboard to detect and quantitate new toxic elements. Experience has shown that many of the so-called "new" elements have existed previously in conventional submarines, but were either not recognized or were quite properly disregarded, since significant concentration values were not obtained with the limited submergence times of the pre-nuclear period.

Many traps await the unwary in trying to forecast presence or degree of importance of a given toxic substance in such a finite environment. An example is that of carbon monoxide, the production of which was previously linked chiefly to diesel exhaust fumes. With the passing of diesel propulsion one might expect this problem to be minimized. On the contrary, tolerance concentrations (100 parts per million) have been reached within thirty hours submerged on nuclear submarines. The chief source now is tobacco smoke, a source not previously emphasized, yet of extreme importance with longer periods of submergence.

Another example of an apparently harmless product giving rise to trouble in this new environment is the evolution of radioactive radon gas originating from luminescent radium-painted markers. It has been standard practice for many years in our submarines to use radium-painted markers and dials for emergency illumination. Such radium, of course, will produce its radioactive daughter-gas, radon. Gaseous radon diffuses easily from apparently well-sealed components and enters the ship's atmosphere. Here it proceeds to decay into a long series of radioactive daughter elements which become associated with dust particles suspended in the air. They are then easily collected by the filtration devices which operate constantly to monitor the air for air-borne radioactivity. Fig. 1 shows a rather dramatic increase in air-borne beta activity with time submerged as the result of only six small radium-painted switch markers being present on the submarine. Note the abrupt increase in air activity after submerging—a factor of more than ten in twenty-four hours. The curve shows the gradual levelling off as equilibrium is approached in about forty-eight hours. At equilibrium, levels are about thirty times higher than when surfaced. Apart from possible biological hazard this represents a serious nuisance because radiation monitoring equipment does not distinguish between such increases due to radon and that due to the much more serious condition of a reactor system leak. One would be justifiably quite concerned by such an increase if due to a reactor system leak. It is, therefore, necessary to initiate an immediate and complicated identification technique whenever such increases occur. The only solution is to remove all such radium sources from the ship, and, indeed, from the entire navy supply system to avoid their reappearance on board. The lower interrupted curve in Fig. 1 shows the increase in air activity over a similar period after removal of the six small markers. The remaining concentration is chiefly due to the radium-painted dials on the wrist watches of crew members.

These problems, and others like them, have been solved for the most part by removal of the offending source, by insistence on more rigid leak tightness requirements in systems containing toxic materials or by substitution with less toxic materials, and by development of removal systems such as the $CO_2$ scrubber. In the design of removal equipment medical personnel have a vital contribution to make. They must furnish the design engineer with the desired allowable concentration of the toxic substance. In the case of carbon dioxide, for example, it is not feasible to build equipment which will sustain zero concentrations; a

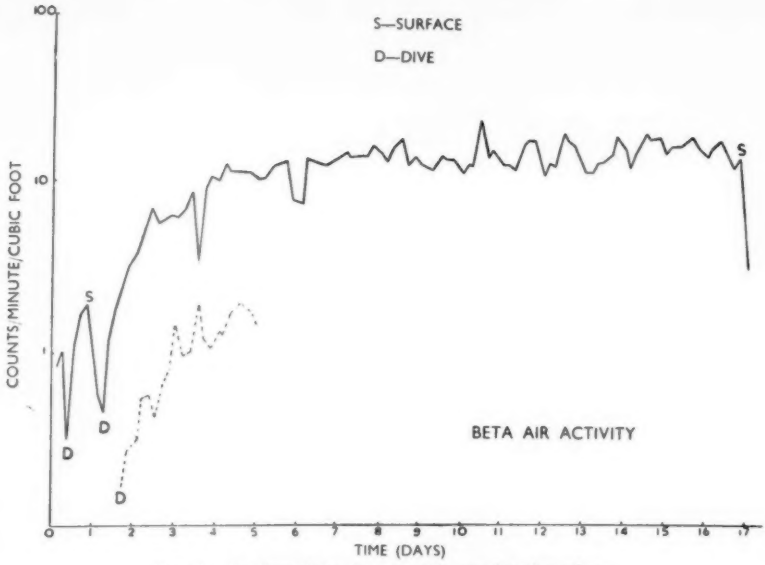



FIG. 1.—Radioactivity due to radium-painted markers.

compromise tolerance concentration must be used. Such tolerance concentrations, however, cannot be based on standard tolerances in the literature which apply usually to the eight-hour day, five days per week exposure time of industry. Aboard submerged submarines, where a 24 hours per day exposure is the case, lower tolerance limits must be applied. This principle equally is related to maximum permissible values for radiation levels as well as for toxic gases. It is, thus, one of the prime missions of submarine medicine to establish such limits by investigation and research and to communicate them to the design engineer.

The environmental factors at work here may equally apply to space medicine, and indeed, in many respects, one might simply substitute "space ship" for "submarine" in this discussion.

## RADIATION IN THE SUBMARINE ENVIRONMENT

Radiation hygiene in a submarine, an environment radically different from that of land-based reactors, presents the necessity of adapting and modifying standard control techniques. In many respects this novel environment is hostile toward efficient radiation hygiene. The following five factors, for example, will all operate to increase the shipboard radiation control problem:

(1) The closed atmosphere of a submersible allows for little dilution of air-borne radioactivity by dispersion in air.

(2) Lack of space for such requirements as decontamination stations and control areas.

(3) Proximity of living, eating, and food preparation areas to an operating reactor system with an ever-present potential contamination hazard.

(4) The submariner's work week, which is a seven-day week with no possible off-site recuperation from exposure.

(5) The constant and relatively rapid re-circulation of air through the ship's ventilation system when submerged allows for rapid spread of air-borne radioactivity from one spot to another.

If, however, one examines a submarine more closely there are many inherent factors, particularly in its architecture, that will tend to assist radiation control. First of all, the submarine is arranged horizontally like a long sealed tube. The reactor compartment section of the tube, the chief source of radiation, can affect personnel only within the compartment itself or immediately forward and aft of it. Shielding is thus simplified and the advantages of locating living areas with zero radiation levels either well forward or aft of the compartment, exploited. As far as the crew is concerned shielding in three planes only is vital, and full circumferential shielding of the system is not necessary.

An additional important factor is that our sealed tube is horizontally divided into a series of compartments by stout watertight bulkheads. This allows for rapid isolation of a given

contaminated compartment simply by shutting a watertight door and securing ventilation to that area. In the case of the reactor compartment, ventilation supply and exhaust lines pass through the compartment without openings into it. Since this is the potential area of contamination, pick-up by the ventilation system can be avoided. (Fig. 2).

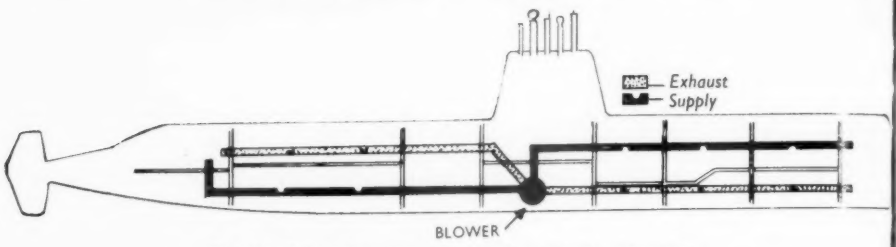



FIG. 2.—Submarine compartmentation and air recirculation.

Additional helpful factors are the small number of personnel in a submarine crew, which allows for ease of communication and control, and lack of multiple exits and entrances that must be guarded by monitoring stations in an industrial plant.

These advantages and disadvantages can be manipulated into an effective shipboard programme. For example, contamination control is built around the compartmentation system and its ease of isolation; occupancy of the reactor compartment is held to a minimum by placing master controls outside this area; contamination casualty regulations require rapid shutdown of the re-circulating ventilation cycle; protective clothing is dispersed fore and aft of the engineering spaces for accessibility.

Apart from control techniques themselves, considerable adaptation of radiation equipment is also necessary and laboratory techniques used on board must be modified to meet the peculiar environmental situation of a submarine. Radium calibration sources are prohibited due to the radon problem mentioned previously and cobalt 60 is substituted as a calibration source. Again, because of the explosion hazard and high oxygen consumption, open flames cannot be tolerated and evaporation of liquid samples must be done by infra-red lamps. Evaporation of large twenty-four-hour urine samples as a check on ingested activity is prohibited for æsthetic reasons in the confines of a submerged submarine, and must await an in-port period. At sea it would be done only on an emergency basis with an assured lowering of the popularity of medical department personnel among the crew. Volatile solvents in radio-chemical techniques must similarly be avoided. All radiation-measuring equipment must be rugged enough for use on board an operating combat ship, a requirement which, surprisingly, disqualifies many devices used in a shore-based installation.

One interesting technique modification is in the use of an end-window Geiger-Mueller tube for counting of liquid samples. In this a carefully measured 50 ml. aliquot of the liquid, usually reactor coolant water, is placed in a standard metal cup. The cup is positioned on a shelf beneath the Geiger tube. Accurate positioning of the cup in relation to the tube is important and is carefully checked with standard spacers and positioning pins. Under these fixed geometrical conditions the number of counts per minute obtained by counting the sample may simply be referred to a predetermined calibration curve of counts per minute versus microcuries per millilitre. If the calibration curve is based on an isotope whose energy approximates that of the sample very accurate results can be obtained to a level of $1 \times 10^{-5}$ microcuries per millilitre. This is a simple, rapid technique and has the advantage of quickly being taught to untrained personnel. It was soon observed that in rough seas spillage from the cup would result from this procedure. Under such conditions the cup is covered with a thin film of Saran wrap, a cellophane-type material held firmly in place by a metal lip or rim which fits over the cup. Sensitivity loss when utilizing this is 10%, a reduction to $1 \times 10^{-4}$ microcuries per millilitre as the lower limit of detection.

These are only a few of the necessary modifications to standard techniques, and, as in the case of radiation control procedures, the submarine milieu is all-important in determining the degree and type of modification necessary.

## THE REACTOR

Before discussing the personnel exposure problem aboard nuclear submarines it is necessary to describe the reactor system.

A water-cooled reactor may be considered simply as a collection of uranium atoms. Bombarded by neutrons, the uranium atoms fission, or split, and release a tremendous

amount of radiation and kinetic energy as heat, which can be removed by water flowing through the reactor lattice. The two atomic fragments remaining after the parent uranium atom is split are the fission daughters, and are intensely radioactive, emitting both gamma and beta radiation. These fission daughters cause *residual reactor radiation* long after the reactor is shut down. The reactor, then, is responsible both for prompt fission radiation (gamma and neutron) and residual radiation (gamma and beta). These are not the only sources of radiation for the reactor as it operates produces high levels of neutron radiation in its vicinity. These reactor neutrons will activate stable non-radioactive atoms present in the coolant water flowing through the reactor lattice.

As water flows through the reactor the temperature of the water is raised by the fission process and this heat, in turn, is transferred to a steam generation system through a heat exchanger or boiler. The reactor coolant water leaving the heat exchanger is then propelled back through the reactor by a pump. This closed cycle operation of coolant water is illustrated in Fig. 3. There are two important points to note about this system—first, the

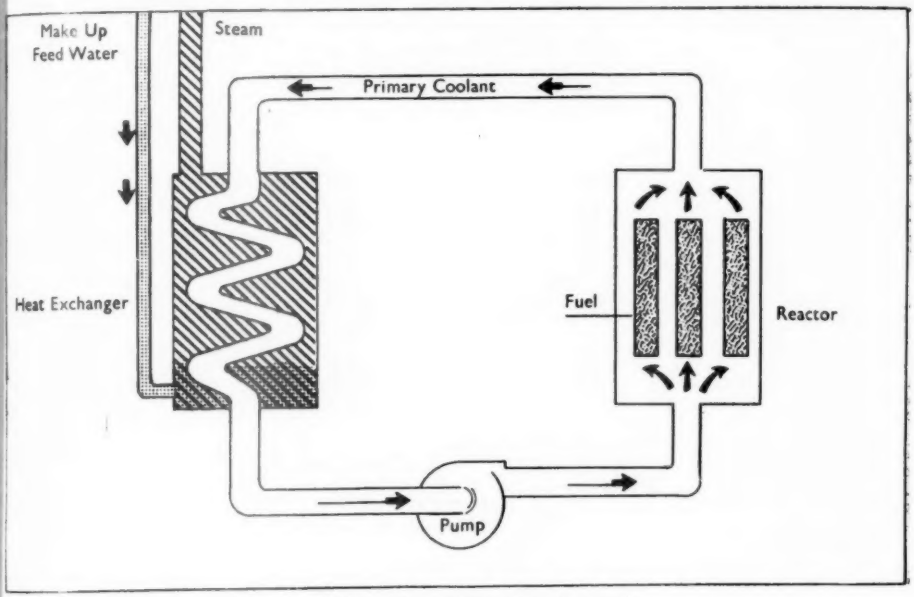



FIG. 3.—Basic reactor system and coolant cycle.

piping carrying this coolant water is leakproof; secondly, the steam generated in the heat exchanger is not radioactive. Note that the radioactive coolant water "sees" the steam only through the walls of the heat exchanger; there is no direct contact between radioactive water and the steam. This steam can thus be easily transferred from the reactor area without shielding and can be used to turn a conventional steam turbine.

Circulating in the coolant water are the neutron-activated radioactive atoms we have mentioned previously. The metallic radioactive atoms will tend to stick on the inner surface of the piping, an important phenomenon, having an effect both in raising radiation levels in the area, and in necessitating precautionary measures for contamination control whenever the system piping is opened. These radioactive atoms in the system piping continue to radiate after the reactor is shut down, and they are chiefly responsible for the gamma radiation levels in the compartment at that time. The residual fission radiation from the fission daughters in the reactor itself, being well shielded, makes little contribution. In the case of the longer-lived radioactive atoms in the coolant water, there will tend to be increasing build-up with time so that static conditions will not be met in regard to radiation dose in this area, but will tend to increase.

The compartment containing the reactor system is a section of the submarine termed the reactor compartment. This compartment, essentially a right cylinder, is divided horizontally by a deck forming an upper and lower reactor compartment. The deck is actually a thick shield, below which is placed the reactor and all the coolant system (Fig. 4).

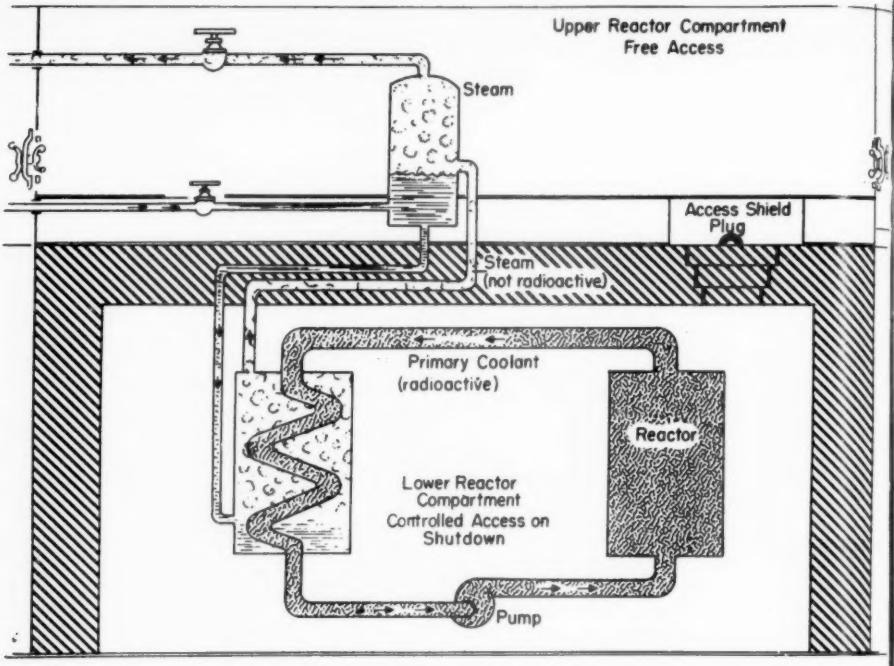



FIG. 4.—Reactor and its shielding.

Note from Fig. 4. that the upper reactor compartment sees no contaminated coolant water, only non-radioactive steam. Some gamma and neutron radiation will enter the upper level through the shield when the reactor is operating, but not in any degree which prohibits working in or manning the upper compartment. The highest level of radiation in the upper compartment is above the reactor area and sharply falls off with distance from that point. Levels in the after section of the upper compartment at full power, for example, are of the order of only 5 mrem per hour.

It must be emphasized that the reactor compartment is the only area on the ship where a radiation flux exists. All other compartments are similar to those on conventional submarines. Outside of the reactor compartment, crewmen, when submerged, receive less radiation than when ashore, due to the shielding effect of the water on cosmic radiation. This effect is noted on background radiation which decreases to a third of surface values with increases in depth of the submarine.

To return to the lower reactor compartment—the majority of the radioactivity in the coolant water has a short half life, and, because of its rapid decay, the lower area can be entered after reactor shut-down. While some reactor residual radiation remains, the chief source of radiation is gamma from the "plate-out" activated atoms inside the piping. Normally, there will be no exterior contamination present unless the system has been opened previously and contaminated coolant water spilled. Prior to entry into the lower reactor compartment after reactor shutdown, ship's personnel are preceded by medical department members who survey and monitor the area, checking for surface contamination, air-borne radioactivity, and degree of potential exposure. Permissible stay times in the lower compartment are determined and requirements for protective clothing formulated from this information. Monitoring stations are also established at exit points from the compartment and personnel leaving the area carefully checked for contamination. The monitoring points are also used as change areas if protective clothing is required.

## RADIATION EXPOSURE LIMITS—THEIR MEANING

One of the often misunderstood aspects of radiation exposure is a faulty concept of maximum permissible exposure levels, particularly in relation to presence or absence of clinical findings. In dealing with any potentially toxic material industrially, be it lead,

organic solvents, or radiation, it is necessary for operational purposes to compromise between zero exposure and the levels known to cause detectable biological effects. This compromise value, often called tolerance, is usually placed well below the threshold of minimum clinical change by a large factor—providing a threshold clinical response is typical of the toxic element in question.

In arriving at such a maximum permissible value, one uses historical observations, human clinical data, animal experimentation and laboratory data. For continuous industrial application the permissible exposure arrived at must be well below the threshold known to produce detectable change even if the exposure should last over the entire work life of the individual. This is usually accepted as being thirty years in duration.

Since for many clinical effects the rate of exposure is equally as important as the total integrated amount received over a given period, permissible levels may be expressed in terms of a rate. In the case of radiation the rate of total body exposure rather than the total dose is the more important, except for genetic, and possibly longevity effects, For example, 40 roentgen of total body gamma radiation received over a period of eight years will produce no effect on hæmatology of the individual, yet the same dose, if delivered in minutes, will produce demonstrable findings. In this latter case the time-dose relationship is such that the rate of tissue regeneration is exceeded by the rate of tissue damage.

The permissible exposure basically used in shipboard shielding design is 300 mrem per week measured in air. Note that this is not a wartime, or single emergency, or casualty exposure, but an industrial type application for continuous operation over a work lifetime. If 25 to 40 rem total body radiation is required as the threshold dose to initiate leukopenia—one of the most sensitive of biological indicators—it is obvious that one cannot depend upon clinical laboratory procedures to control radiation exposure at or below the 300 mrem/week tolerance level. In the hæmatological example the threshold of a sensitive biological indicator is 150 times greater than the maximum allowable weekly exposure of 300 mrem, far too high to be of any value.

The important and often misunderstood point is that *personnel exposure control and exposure measurement at or below tolerance levels is entirely dependent upon instrumentation. Clinical laboratory procedures are of no value in this regard.* This point is emphasized because of the repeated questions, not limited to laymen, concerning clinical findings in our personnel, particularly in relation to hæmatology. The lack of reality in these questions is obvious when the exposure pattern on "Nautilus" and "Seawolf" is analysed. This point is emphasized because of the potential danger inherent in the false idea that routine blood counts constitute a radiation hygiene programme. If such a programme were mistakenly used as a control measure, gross over-exposure by present tolerance standards would result.

A second point that requires emphasis is that, since permissible levels are well below the biological threshold, cumulative effects by definition cannot occur, since rate of tissue and cellular repair will always exceed rate of damage. Note this holds true only for effects that show a threshold, and does not apply to such non-threshold phenomena as genetic change where cumulative effects can occur independent of rate.

### The Exposure Record—"Nautilus" and "Seawolf"

The preceding statements become more emphatic when the personnel exposure data of "Nautilus" and "Seawolf" are analysed. At the presently accepted permissible exposure of 300 mrem per week, during the fifty-week period of one year a man may receive 15,000 mrem (or 15 rem). Recent recommendations from the National Committee on Radiation Protection may, in effect, officially reduce the weekly permissible exposure to 100 mrem per week. On a yearly basis this would be 5,000 mrem (or 5 rem) per man per year. Bearing the figures of 15,000 and 5,000 mrem per year in mind, note the following average exposures:

(1) "Nautilus" in 1955 .. .. 173 *mrem per man per year*
(2) "Nautilus" in 1956 .. .. 210 *mrem per man per year*
(3) "Seawolf" in 1957 .. .. 204 *mrem per man per year*

"Seawolf" exposure data is extrapolated from data obtained during the first six months of her first fully operational year.

These figures of average yearly individual exposure at their maximum represent 1·4% of the official permissible exposure and less than 5% of the proposed new permissible exposure level.

If rather than the average exposure, the maximum individual yearly exposure is used a wide differential still exists between the actual level and the maximum permissible level. The following represent the highest individual yearly exposures recorded:

(1) "Nautilus" in 1955 .. .. 1,438 *mrem per year*
(2) "Nautilus" in 1956 .. .. 2,100 *mrem per year*
(3) "Seawolf" in 1957 (extrapolated) 1,126 *mrem per year*

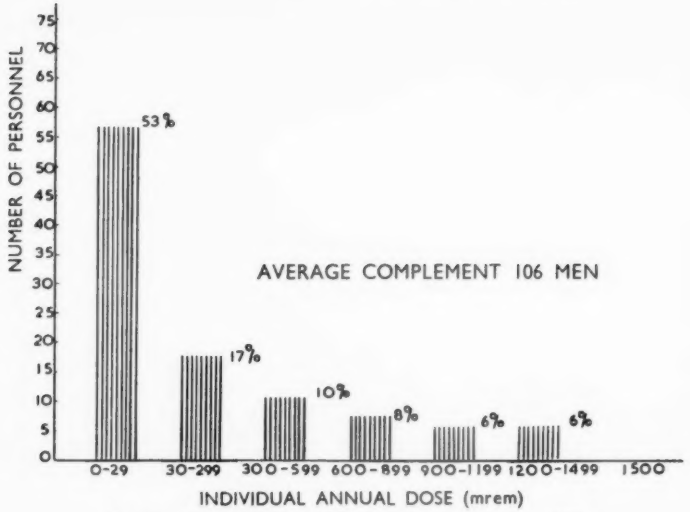



FIG. 5.—Distribution of individual exposure during 1955.

Taking the highest figure, these maximum exposures represent values of either 14% or 44% of the maximum permissible exposure per year.

Fig. 5 illustrates an important pattern of this exposure in depicting the distribution of yearly dose among the ship's population. It should be noted here that almost 50% of the crew receive no measurable exposure. The remainder of the crew spend varying periods of time in the reactor compartment and, therefore, receive some exposure. This is the only section of the ship where exposure can be received due to the conservative shielding practice described previously. The data shown in Fig. 5 is from the 1955 data of U.S.S. Nautilus but has held true since that period for both ships.

This exposure record serves to emphasize the fact that all of our experience to date is well below both the level of clinical effect and of maximum permissible exposure values.

## INSTRUMENTATION

In the absence of any dependable clinical effect to quantitate human exposure our dependence upon instrumentation is great. The data given above, for example, were obtained from personnel film badges worn by all hands on board. Such personnel exposure is measured both by the film badge and pocket dosimeter. The ship maintains its own photodosimetry programme, including capability for full processing of the film badges. Radiation monitoring equipment, counter-scalers for sample counting, radiochemical equipment, radiation sources, film processing tanks, and other equipment are located in a small, compact laboratory under medical department cognizance duplicated in both ships. Figs. 6 and 7 show views of the laboratory. In addition to the concentration of analytical equipment in the laboratory, protective clothing, including filter masks and emergency radiation measuring devices are dispersed throughout the ship.

It has been emphasized that these instruments, rather than any known biological changes, are required to quantitate personnel radiation exposure at the sub-threshold levels encountered in nuclear submarines. Such equipment may appear deceptively simple in operation but requires a thorough knowledge of its limitations, capabilities, and eccentricities for maximum usefulness.

Let us analyse some of the general problems associated with personnel dosimetry in order to point out the pitfalls in using instrumentation. Consider, for example, the film badge and pocket dosimeter. These devices are worn by all the ship's personnel when aboard and form the basis for personnel exposure records. The film badge is a metal holder, divided into a shielded portion and an open window portion. This division of the badge into two sections allows the film contained in the badge to differentiate between beta and gamma radiation by the response of the portion of the film below the shield compared to that below the open window. This also allows for some differentiation of thermal and fast neutrons if the shield is cadmium or some other element which captures thermal neutrons. In the case of beta-



FIG. 6.—Radiation laboratory.

gamma radiation the film, after developing, presents a density proportionate to the amount of radiation seen. The degree of density of the emulsion is determined by a densitometer, and the density obtained referred to a density-dose calibration curve. The calibration curve itself is based upon exposure of several films to a known standard radiation source, determination of the density for each known dose, and plotting the results as a curve. Such a curve must be made on each batch of film used.

The pencil-like pocket dosimeter is a device much like a simple gold leaf electroscope. When held up to light a fibre is visible in the eye-piece against a small scale reading 0 to 200 milliroentgen. Ionizing radiation passing through the dosimeter removes an electric charge on the fibre causing it to move across the scale in the manner of the gold leaf in a discharging electroscope. The fibre can be reset to zero by re-charging the dosimeter after any desired time or dose interval. Removal of the charge, and hence a positive reading, can occur due to insulation leakage known as "drift". Usually this is at a very low rate, but must be determined on each dosimeter. Calibration against a standard radiation source is also necessary as with film. A characteristic of dosimeters is sensitivity to mechanical trauma—an important negative characteristic aboard a ship where rough treatment may be expected.

Many variables affect results and influence interpretation in both instruments. In the case of film, storage at recommended low temperatures is important. Film storage must also provide for zero radiation exposure which must be checked by processing control film. Calibration conditions for both devices must be carefully considered, including freedom from backscatter. Both film and dosimeters are energy-dependent, and for this reason the calibration source must emit energies approximating those to be met in the field, a difficult achievement. In the case of dosimeters, the drift rate must be repeatedly checked as insulation properties may change with time and environmental conditions.

If it is assumed that all of these factors have been adequately controlled, many important variables remain to be considered. First of all, both these devices will usually be worn

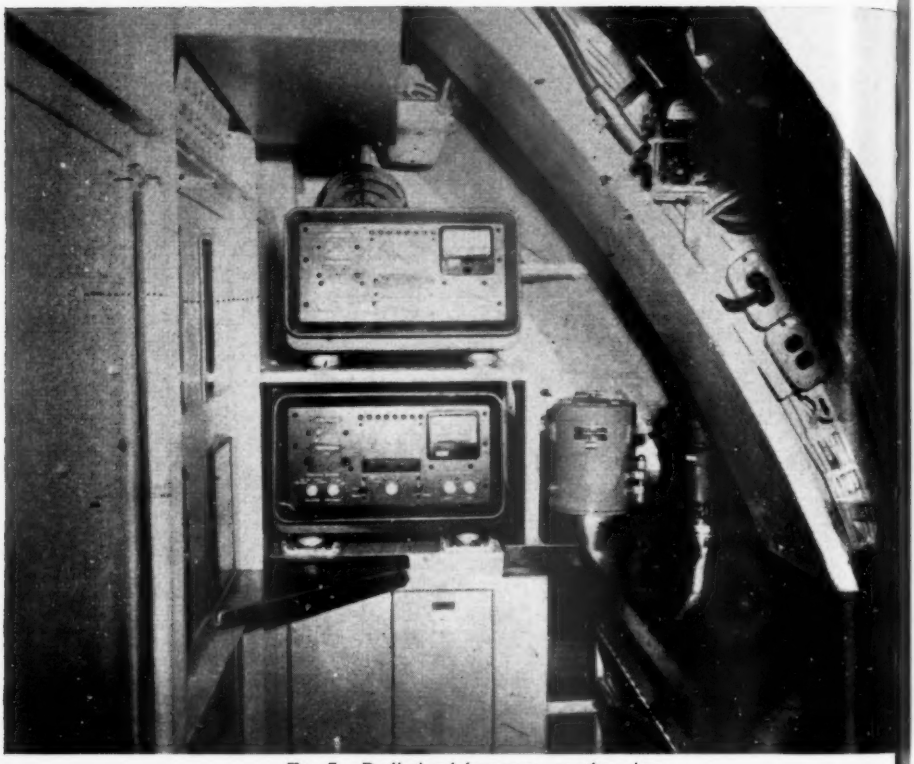


FIG. 7.—Radiation laboratory; another view.

clipped to the shirt front. In this position they do not measure a pure air dose as required by definition of the roentgen, but a complex dose disturbed by body backscatter. While one may minimize this factor by calibrating with a phantom, the angle of incident radiation in the field may differ significantly from that of the calibration situation; this is not a predictable variable within accuracy limits in the shipboard situation, but varies from position to position and with the attitude of the wearer.

If these factors are accepted, one faces an important problem in interpretation of the depth dose. The film badge is worn on the body surface and, as such, measures a surface dose which will be significantly modified by several centimetres of tissue before reaching a depth such as the median sagittal plane. The relationship between surface and depth dose can be computed, but the relationship will vary markedly with the energy of the radiation, with variation in tissue density due to presence of bone or air, and with angle of incidence of the radiation among other factors. A specific instance of large error, for these reasons, exists in those cases where the primary radiation enters posteriorly and the devices are worn anteriorly, a practical situation in lower reactor compartment work. An additional factor lies in the fact that, while total body exposure is the entity of interest, only a few square inches of body surface is covered by the film badge and dosimeter. A narrow beam may, therefore, be missed entirely, or, if detected, will be over-emphasized in relation to total body exposure.

If all of these possible variables and conditions are accepted, one is still faced with even further variables in the technique of film processing itself. These include control of purity of water used in mixing processing solutions, adequacy of darkroom conditions, and control of solution temperature during processing. Temperature control alone is a formidable problem and must be maintained rigidly throughout the processing solution with avoidance of any layering effect because temperature changes during processing will affect the emulsion as well as radiation.

Considering all of these many variables inherent in only two of the instruments used it

is not surprising that there is a search for some concrete biological change as a means of quantitating exposure to ionizing radiation. Interpretation of data obtained from such equipment requires a broad knowledge of both physical and biological factors. This is probably the strongest argument for the utilization of a medical officer in this field. Radiation is not an entity whose hazard can be simply evaluated by a glance at a meter or recording of a number, but requires careful consideration of many physical and biological factors. This is particularly important as a result of recent trends toward lower permissible exposure values, as instrument accuracy becomes more strained at the lower limits of sensitivity.

## Medical Department Duties

The medical departments of both ships consist of a submarine medical officer and two hospital corpsmen, although more corpsmen may be assigned from time to time for training purposes. The medical officer, besides his regular submarine medicine training, will have received at least an academic year of training in nuclear medicine, and will usually have had several months' experience at an operating land-based reactor prototype. The corpsmen have received at least nine months of training in radiation hygiene techniques, and also participitate in the course in nuclear engineering given to all engineering ratings.

While at sea one of the three members is on watch in the laboratory at all times. During his watch he is responsible for following a schedule of various radiation checks. For example, every four hours portable air samples are taken in the engine room and reactor compartment and processed in the laboratory, several check points in the reactor compartment are spot-monitored for gamma and neutron radiation levels as a check on shield integrity, constant monitoring equipment through the ship is checked, read, and recorded every watch, liquid samples from various portions of the engineering plant are processed and counted on a watch basis in order to maintain a constant record of radioactivity present. All radiation measuring devices must be checked daily for accuracy with standard radiation sources. Weekly, all compartments are wipe-sampled as a check on surface contamination. Every two weeks personnel film badges are collected, processed, and results recorded. When submerged, in addition to the radiation measurements, determinations of oxygen, carbon dioxide, carbon monoxide, and other gases are made every two hours.

During in-port periods if work is scheduled in the lower reactor compartment, particularly if disassembly of the system is involved, the workload increases markedly. For, in such a period, the control of contamination in the confined space of a submarine represents a great challenge. In such a period monitoring points must be manned, work times determined in radioactive areas, protective clothing requirements decided upon, and transport of contaminated material supervised. Decontamination facilities may have to be established. The situation is never static. Each task requires its own analysis and solution.

## The Future

The problems of the future with the expansion of the nuclear navy are:

(1) Need for extensive training of personnel and development of shore-based facilities for handling repair and maintenance of nuclear ships, especially in processing of contaminated equipment on the ship and on the base; establishment of dosimetry and monitoring facilities for contaminated laundry; use of material decontamination techniques.

(2) Development of more accurate instruments for relating radiation measurements to true biological dose, particularly in the field of neutron flux measurement.

(3) Development of long-term training programmes for both officer and enlisted medical personnel in the field of radiation hygiene.

(4) Continuing research on the effects of prolonged submergence, particularly in the identification and quantitation of all atmospheric elements built up under such circumstances.

But these are problems limited to the navy where nuclear power is in being rather than in potentiality—what of the significance to the civilian medical profession as a whole? A recent article in *Nucleonics* magazine, demonstrates the dramatic increase in the number of operating civilian reactors by 1960. With such acceleration medical problems are bound to appear in this area, and can potentially involve all of us, if in nothing more than in allaying the chronic semi-hysterical outlook of the public in any matter concerning nuclear radiations.

Nuclear power is the most promising development to meet the challenge of diminishing fossil fuel supplies. The events in the Middle East stress the World's dependence upon fossil fuels and the consequences of any diminished supply of them. Yet, diminish they must, and at a rapid rate by the early twenty-first century, with consequent lowering of industrial potential and standards of living if substitutes are not available. Great Britain has already launched a large-scale civilian nuclear power programme.

Specifically, the physician interested in industrial medicine will be deeply involved in evaluating and establishing future radiation control programmes, the traumatic surgeon may find wound contamination a new factor, the ophthalmologist will be used in physical

screening of personnel for posterior subcapsular opacities, the internist will be involved in diagnostic problems, not the least of which may be emotional in origin in relation to radiation; hæmatologists will also play a part.

We must not, then, consider this a limited field, confined to a handful of military specialists; but a field of potential future significance to us all. Apart from the specialized problems mentioned, the profession should be cognizant of this technology and its effects simply to answer the questions from a public beleaguered with conflicting statements related to weapons and weapon effects, so often confused with reactor radiation problems.

It would seem prudent to incorporate such subject matter into medical school curricula as soon as possible, and perhaps into present industrial medicine courses, perhaps as part of radiology, by any method which will assure our capability of dealing with the problem.

### Discussion

In reply to a large number of questions by **Squadron Leader T. C. D. Whiteside, Air Commodore D. A. Wilson, Dr. B. W. Soole, Rear-Admiral G. A. M. Wilson, Dr. D. W. H. Barnes, Mr. D. E. Barnes, Professor G. P. Crowden, Surgeon Captain C. B. Nicholson** and others, **Lieutenant-Commander Ebersole** said that body odours were overcome largely by the use of the filtration units already installed for removing $CO_2$ and CO from the atmosphere and by the submarine's ventilation system. The crew also became immune to the residual submarine odour during a long cruise, although others became aware of it when they went ashore. Dispensing with diesel propulsion had not changed this characteristic submarine smell which permeated clothing and was probably contributed to by a number of chemical factors which had not as yet been identified.

He was convinced of the need for the Naval Medical Department to be given full responsibility for the control of the environmental factors, including the radiation hazard, which were encountered during prolonged submergence in nuclear-powered submarines especially during the developmental period. This allocation of responsibility might not hold, however, for nuclear-propelled surface ships. The engineers had their hands full with their own technical problems in submergence and it would be unfair to expect them to give the necessary weight to the human factors which these obviously merited; and they might at times "rush in where angels fear to tread!" The commanding officer needed the authoritative advice of a medical officer who was technically familiar with the many complex problems involved, particularly as the total situation had not yet been evaluated.

In the United States Navy submarine medical officers and hospital corpsmen were trained in submarine physiology and plant construction as part of their initial course of instruction before they volunteered for nuclear-powered submarines and underwent further training. They had to know the component parts of the engineering plant and even to take part in routine watchkeeping duties. This additional training had paid off time and again during the development stage and early operations of U.S. Submarines Nautilus and Seawolf.

In reply to Dr. Soole Lieutenant Commander Ebersole said that saturated caustic soda was used for fission product analysis in place of ammonia hydroxide—a nasty substance to handle in a rolling submarine. Mineral acids were substituted for volatile organic acids such as glacial acetic acid. Pulse height analysis was not used for identifying specific isotopes. There were at present difficulties in the use of scintillators which might be overcome.

The neutron problem was first tackled by the contractor who was required to shield the reactor to ensure that not more than 10% of the radiation dosage was due to neutrons. The B.F.3 tube instruments for thermal neutron estimation and Radioactive Products Incorporated Model E.1 fast neutron dose rate meter were used as routine monitoring instruments. Neutron film badges (Eastman Kodak N.T.A. emulsion of 40 micron thickness) were always worn but they were only developed if the gamma dose exceeded 200 mr in a two-week period.

Neutron film development was more complex than estimating gamma dosage, as it involved the use of a microscope and oil immersion techniques.

In reply to Dr. Barnes he showed a picture of the ship's sick bay which was kept quite separate from the radiation laboratory. There was, however, very little sickness in submarines apart from the customary respiratory epidemics at the beginning of a cruise before the crew became immune to each others' strains. The number of injuries sustained on the bridge on the surface in conventional submarines was greatly reduced in nuclear-powered submarines which spent very much longer periods submerged.

In reply to Mr. Barnes he pointed out that radiation dosage was not a function of the shield entirely, as the greater exposure occurred during maintenance periods when men were beneath the shield. Little was to be gained by shaving a small amount of lead off the shield under existing circumstances, especially as at a later date the submarine might well be required to carry a large amount of lead ballast when it went to sea, a fraction of which could have been incorporated in the shield. There would be a gain from reducing the size of the reactor compartment but this would also reduce the accessibility of the component parts within it.

The effects of long-term exposure to carbon dioxide had been investigated before "Nautilus" did a prolonged dive in a submarine hull moored alongside in New London. Upwards of 20 men were exposed to 1·5% $CO_2$ in air for six weeks without any gross ill-effects being observed. But, the ideal was to provide the submariner with air that approximated to atmospheric air in composition as nearly as possible. In his opinion 1% $CO_2$ was a far better upper permissible limit to consider, particularly if smoking was to be allowed, for carbon monoxide potentiated the effects of carbon dioxide.

In conclusion, the **President** thanked Lieutenant Commander Ebersole for his most valuable address and for coming from the U.S. Submarine Seawolf to speak to the Section.

# Section of Psychiatry

President—Professor E. STENGEL, M.D., M.R.C.P.

[*October* 8, 1957]

## Reflections on the Undergraduate and Postgraduate Teaching of Psychiatry [*Abstract*]

PRESIDENT'S ADDRESS

By Professor E. STENGEL, M.D., M.R.C.P.

*London*

THE quality of general practice as well as the future of psychiatry depends a great deal on the undergraduate teaching of psychiatry which varies considerably in this country. To take the example of the two Yorkshire universities, the Department of Psychiatry at Leeds was established soon after the end of the war, while the Department at Sheffield is still *in statu nascendi*. However, the Sheffield medical students are already getting some psychiatric teaching throughout the clinical part of their curriculum. They meet the Professor of Psychiatry during their introductory clinical course, in the study of social medicine, during their periods of medical clerking and in the study of gynæcology and obstetrics. They attend the psychiatric in-patient unit once a week for three months. This attendance is to be replaced by a month's clerking shared with neurology. There is, in addition, a course of lecture demonstrations extending over two terms ending with an obligatory written and clinical examination. There is a short pre-clinical lecture course in psychology. Difficulties arise from shortage of teaching staff. In spite of these efforts psychiatry remains foreign to the student who has received hardly any basic teaching relevant to it when he starts on his clinical course which he tends to regard as an application of his pre-clinical studies. It seems essential that "the person" should be introduced from the beginning of the pre-clinical course, as was advocated by A. Meyer long ago and is now widely practised in the United States. Only when the student learns about human development and behaviour from the psychological and social aspect side by side with anatomy and physiology, will he be able to integrate psychiatry with the rest of his medical training.

Postgraduate teaching in psychiatry presents serious difficulties in the provincial medical schools. A number of universities have been running diploma courses modelled more or less on that of the London Institute of Psychiatry which is concerned with postgraduate teaching only. Some of these courses are providing systematic instruction qualifying for internal diploma examinations. They have proved a severe liability to the small university departments whose main function is undergraduate teaching. They cater for a few postgraduate students, while the majority of those in need of instruction get nothing from the universities. The number of diplomas (10 in the British Isles) is excessive. They are competing for candidates some of whom feel compelled to work for two diplomas for periods of time, an unhealthy state of affairs. The role of the postgraduate medical schools in London and their possible contribution to the needs of the rest of the country is discussed, with special consideration of psychiatry. At Sheffield no attempt is made to offer systematic courses, but only weekly seminars relevant to basic and clinical psychiatry and aiming at helping the student with his studies. It is regarded as essential to mobilize the latent teaching potentialities of the mental hospitals. In every hospital which has staff in need of postgraduate training one of the consultants is to be given the function of "Advisor in postgraduate studies" who acts as liaison officer with the university department and organizes conferences, &c., within the hospital. This scheme, which has the active backing of the Sheffield Regional Hospital Board, aims at breaking the educational isolation of the young psychiatrist not working in the university centre and at spreading the responsibility for postgraduate education fairly, instead of leaving it entirely to the university department which is unable to carry it alone, without detriment to its other commitments.

REFERENCE.—MEYER, A. (1948) Training the Doctor. The Common-sense Psychiatry of Adolf Meyer. Edited by E. Lief. New York.

(To be published in full in the *Journal of Mental Science*.)

[*November* 12, 1957]

## DISCUSSION ON PHYSIOLOGICAL MEASUREMENTS OF "EMOTIONAL TENSION"

**Dr. Brian Ackner** (London):

In the everyday currency of our language we do not seem able to do without the coin "emotion", but for scientific purposes it cannot be considered to be valid currency. There is no such *thing* as emotion, it is an abstraction derived from certain subjective mental states and associated behavioural and bodily changes. However, although the concept of emotion as such cannot be the object of scientific investigation, reportable subjective mental states and observable behavioural and bodily changes seem to be reasonable fields of enquiry.

James, in his "Principles of Psychology" in 1890 said:

"Our natural way of thinking about these coarser emotions (grief, fear, rage, love) is that the mental perception of some fact excites the mental affection called the emotion and that this latter state of mind gives rise to the bodily expression. My theory, on the contrary, is that the bodily changes follow directly the perception of the exciting fact and that our feeling of the same changes as they occur is the emotion."

The James-Lange theory is no longer acceptable but its predecessor is still implicit in much of our everyday thinking. We still talk about anxiety causing bodily changes, anxiety bringing on an attack of migraine and so on. Our tacit dualism still credits the immaterial with acting on the material. For the purpose of scientific investigation emotional states should be regarded as subjective epiphenomena which may occur concomitantly with bodily changes, both being accompaniments of stressful adaptations.

If both the subjective states and the observable changes arise from a common cause it could be hoped that a full knowledge of one would provide us with some understanding of the other two. However, we cannot satisfactorily quantify the subjective state, and the behavioural expression of emotion is affected by cultural factors and influenced by the immediate environmental situation. We do not even know to what extent the various bodily changes are intercorrelated and whether changes in one field can be reliably accepted as evidence of changes in others. Nor can we quantify "emotional stress" which is dependent on factors both without and within the individual. We can expose subjects to comparable stimuli or environmental factors, but it is the significance of the latter to the individual which determines whether at any particular time they will be stressful or not.

In a study which has previously been reported, an attempt was made to overcome some of these difficulties in the following way. A group of patients was selected on the basis of subjective complaints, appearance and behaviour, all of which left no doubt that the term "severe anxiety", as generally used, appropriately described an aspect of their emotional state. In other words, this was a markedly anxious group as judged by both the common internal and external criteria. This group was compared for experimental purposes with a normal control group and another patient group, in both of which it was considered that the internal and external criteria of anxiety were absent. Instead of trying to induce and quantify stress, the opposite was attempted, namely the absence of stress by means of barbiturate-induced sleep. A number of physiological variables were recorded but particular attention was paid to changes in the amplitude of the pulse volume wave as recorded by the finger plethysmograph. Anxious subjects tend to manifest a relative peripheral vasoconstriction but the tendency is only a statistical one. It seemed possible that sleep might release a stress vasoconstrictor factor and that under suitable experimental conditions this would be manifested by the occurrence of a greater degree of vasodilatation in the anxiety group than in the other two groups. Thus, rather than vasoconstriction, perhaps the tendency to vasodilatation during sleep might be found, under suitable conditions to differentiate between markedly anxious and non-anxious subjects.

The technique and findings of this work have been described in detail elsewhere (Ackner, 1956). The results revealed that the three groups differed significantly in the size of the pulse volume during the resting state and in the increase occurring during induced sleep. The marked pulse volume increase in the anxiety group distinguished the subjects in this group from those of the other two groups.

It seemed profitable to attempt to correlate these findings with the findings of another test which also used barbiturate sedation in the study of anxiety. Shagass (1954) has described a test which he named the "sedation threshold". Starting from the observation that the more tense a patient the greater the quantity of sedation required to produce a relaxing effect he deduced that it would follow that the amount of sedative required to attain a specified end-point of sedation could be taken as a quantitative index of degree of tension. His method

was to inject intravenously Sodium Amytal at the rate of 0·5 mg. per kg. body weight every 40 sec. the subject being asked 25 seconds after each injection to repeat 5-6-7, 77, Massachusetts, &c. The sedation threshold was defined as the amount of Sodium Amytal in mg./kg. body weight required to produce an inflection point in amplitude curve of the EEG frontal 15–30 c/s activity; the inflection point must occur within 80 seconds of the clinical observation of slurred speech.

In a series of publications, Shagass has developed and expanded the application of the sedation threshold test and I shall describe briefly the way in which he has successively revised the interpretation of his findings.

The sedation threshold was first found to be correlated with "tension" as judged clinically, using neurotic and control subjects. Subsequently the term "manifest anxiety" replaced "tension" and it was considered that the greatest amount should be found in anxiety states, the least in conversion hysterics with the mixed neuroses intermediate. This expectation was found to conform to the sedation threshold results for different neurotic groups (Shagass and Naiman, 1956).

The majority of the anxiety states were found to have obsessional personalities whilst hysterical personalities, in common with patients having hysterical conversion symptoms, tended to have a low threshold. It was therefore considered that the sedation threshold was correlated not only with the degree of manifest anxiety but also with the hysteric-obsessional personality continuum. This was thought to be in line with Eysenck's introversion-extraversion dimension of personality.

The threshold was not found to be significantly correlated with degree of tension in schizophrenics but the recent acute cases were found to have lower thresholds than equally tense chronic ones. Considering that in "acute psychoses, ego functions are thought to be more impaired than in non-deteriorated psychoses of long duration, in which reparative processes have taken place" the hypothesis was formulated that the sedation threshold was negatively correlated with degree of impairment of ego functions. According to this hypothesis, the greater the degree of ego impairment, the lower the threshold (Shagass and Naiman, 1955). The sedation threshold in various psychotic categories was again found to conform to expectation, the organic cases having the lowest thresholds, followed by the acute schizophrenics, the agitated depressives and the chronic schizophrenics, with the "borderline states" having the highest threshold (Shagass, 1956).

This concept of impairment of ego function is used to explain why very agitated depressives, who are very tense, have low thresholds. Such depressions, which are also named psychotic depressions, are considered to have impaired ego functions whereas "neurotic depressions, providing they do not occur in severe hysterics, should have high ones". The sedation threshold is claimed to distinguish psychotic depressions from neurotic depressions and anxiety states, and to be able to give a good indication of the "immediate response" to E.C.T. (Shagass *et al.*, 1956).

Finally, in one of his latest papers, Shagass (1957) reports that whereas the sedation threshold was thought to be very stable on repeat testing, it is in fact found to decrease in some subjects where the degree of affective disturbance diminishes. Accepting that this must limit its value in the field of diagnosis and personality Shagass states that the sedation threshold "may now be proposed as an objective index of therapeutic change".

In view of the claims made for the value of the sedation threshold and the amount of attention it has attracted, Dr. Pampiglione and I decided to collaborate in an investigation of this test, our aim being to study the relationship of the sedation threshold to:

(1) The maximum vasodilatation occurring during barbiturate-induced sleep.
(2) The affective state of the individual at the time of the test.
(3) The diagnostic category.

Certain modifications of the procedure as described by Shagass were introduced to achieve a greater reliability and objectivity. To familiarize the subjects with the test procedure and reduce test anxiety, a preliminary EEG and plethysmographic test (without barbiturate injection) was carried out within a few days prior to the actual test. To minimize the disturbance due to the actual injection a Gordh's needle was used. This is an intravenous needle with a rubber diaphragm at the end, which after insertion into the vein can be left strapped to the arm. By this means it is possible to wait until the patient is suitably settled and then the injection is begun, without discomfort to the patient, by means of another needle inserted through the rubber diaphragm.

The course of injection was not influenced by the time at which the subject's speech might appear to slur. Instead his verbal responses were registered by means of a tape recorder synchronized with the EEG and plethysmographic record, and the injection was continued until after the patient had ceased to give any verbal responses.

The test procedure was carried out in one room with the majority of the recording apparatus housed in an adjoining room. After the EEG electrodes and finger plethysmographic

cup had been applied, the patient was allowed to relax for a period and then was interviewed by myself and by the doctor assisting with the injection procedure. As judged by his appearance, behaviour and statements about his own feelings at the time, he was rated for "manifest anxiety" on a 0–5 scale (this was not a very satisfactory procedure, but corresponded to the method employed by Shagass).

Subsequently the needle was inserted and at a suitable time Sodium Amytal was injected at a rate of 0·5 mg./kg. body weight every 40 seconds. Dr. Pampiglione was in the adjoining room supervising the recording and being able through earphones to monitor the injection proceedings and I was responsible for the timing of the injections and for making the patient repeat, 25 seconds after each injection, 57, 5-6-7, British Constitution (the latter was considered to be more suitable to our subjects than Massachusetts!). When the patient finally ceased to respond, one further injection was given and then we waited until there was no further increase in the pulse volume or until 3 minutes had elapsed after the last injection. Consciousness was then restored by means of an intravenous injection of Megimide.

Immediately afterwards we attempted to determine the time at which the patient had slurred. Starting at various points, the tape recording was played back on a number of occasions until the decision was jointly agreed by Dr. Pampiglione, the doctor giving the injection, our recordist and myself. The figure on the dial of the tape recorder was then noted and the corresponding figure on the continuous paper recording was found. From this the amount of Sodium Amytal injected at the time of slurring could also be derived.

This determination of the slur point, although made as objectively as possible, was not without some difficulty. Sometimes the speech became thicker, sometimes slower and sometimes hesitant. But we finally decided to define slurring at the first time a definite disturbance of articulation was noted. However, some patients, having slurred, afterwards articulated quite clearly until later they began to slur again. Furthermore, we noted that at times I repeated the words louder and more firmly, and yet at other times my speech actually appeared to slur!

I shall describe our plethysmographic results and Dr. Pampiglione will subsequently report our findings in respect of the sedation threshold. The test procedure was carried out on 56 psychiatric patients and in 51 of these there was a satisfactory plethysmographic record. The figure for the pulse volume increase was obtained by subtracting the maximum pulse volume occurring during the resting period prior to the test, from the maximum pulse volume occurring following the intravenous injection of Sodium Amytal. The resulting figure was then corrected for a standard 5 c.c. finger, the size of the finger tip enclosed within the plethysmographic cup having been measured following the test. In other words the results are expressed as the pulse volume increase in c.mm./5 c.c. finger tip.

It was found that the 0–5 rating scale for anxiety produced too many small groups and so this six-point scale was reduced by combining ratings 0–1, 2–3, 4–5, to give three groups which represented clinically minimal, moderate and marked anxiety. The marked anxiety group had a mean increase of 11 c.mm. and this is statistically significantly greater than the increase in the other two groups. The moderate anxiety had a larger mean increase (5·9 c.mm.) than the minimal anxiety group (4·8 c.mm.) but this difference is not statistically significant.

In the previous study (Ackner, 1956) it was found that an increase of 6 c.mm. or more distinguished a markedly anxious group from a non-anxious patient group. Using this figure in the present study it was found that 11 of the 13 (84·6%) in the severe anxiety group and 9 out of 21 (42·9%) in the moderately anxious group had an increase of 6 c.mm. or more. In the minimally anxious group 12 out of 17 (70·6%) had an increase of less than 6 c.mm.

The figures reveal a number of similarities to those in the previous study. For instance in the marked anxiety groups of both the earlier and the present study the mean initial resting pulse volumes and the mean maximum increase are within a c.mm. of each other (4·8 : 4·9; 12·3 : 11). However, there are some differences between the minimally anxious groups of the two studies. In the present study the mean initial volume is smaller (5 : 6·3), the mean maximum increase is larger (4·8 : 2·3) and 5 out of 17 patients have a pulse volume increase of 6 c.mm. or greater. These differences may be due to the different population studied but there is a possibility that the difference in the two test situations may to some extent be of importance. In the earlier study the patient, after a previous resting test, lay on a couch and gradually went to sleep, usually with the aid of an oral barbiturate. This was apparently a quite unstressful procedure, in fact many patients spontaneously reported themselves as having enjoyed their "rest period". By contrast the present procedure has an element of stress, occasioned by the presence of two doctors and the anticipation of an injection which will impair consciousness. Now it is possible to demonstrate that, even though there may be no subjective or behavioural evidence of anxiety, an anticipatory attitude can cause various bodily changes (e.g. P.G.R. (psycho-galvanic reflex), pulse-rate, respiration, vasoconstriction, &c.) all of which appear to be part of a general alerting reaction. Whilst it is

unlikely that what we call anxiety can occur without these alerting responses being present, such alerting responses need not necessarily be accompanied by the subjective or behavioural features of anxiety. The presence of bodily changes, therefore, does not necessarily record the presence of emotional disturbance.

Under suitable experimental conditions the bodily changes occurring in those whose clinical features fulfil all the subjective and behavioural criteria of severe anxiety, can validly be contrasted with those in whom such criteria are lacking. Anxiety is, however, a concept whose features can be qualified but not quantified. It is, therefore, not valid to attempt to measure anxiety by using objective measures of bodily change.

## REFERENCES


ACKNER, B. (1956) *J. psychosom. Res.*, **1**, 21.

JAMES, W. (1890) The Principles of Psychology. New York.

SHAGASS, C. (1954) *Electroenceph. clin. Neurophysiol.*, **6**, 221.

—— (1956) *Psychosom. Med.*, **18**, 410.

—— (1957) *Electroenceph. clin. Neurophysiol.*, **9**, 101.

——, and NAIMAN, J. (1955) *Arch. Neurol. Psychiat., Chicago*, **74**, 397.

——, —— (1956) *J. psychosom. Res.*, **1**, 49.

——, ——, and MIHALIK, J. (1956) *Arch. Neurol. Psychiat., Chicago*, **75**, 461.


**Dr. G. Pampiglione** (London):

It is commonly believed that emotion causes visceral symptoms and influences the manifestations and course of disease.

A few hundred years ago emotion, the spring of action and conduct, used to sit in the heart, or in the belly, according to either Racine or Rabelais. Nowadays emotion is considered an agitation of the mind (as in the Oxford Dictionary) involving somehow the brain.

Clinical and intuitive methods are the most important sources of hypotheses concerning physiological mechanisms but the establishment of validity of such mechanisms cannot be based solely on clinical examples. Several studies made by physiologists on bodily changes in emotion showed that there is no rigid parallelism between the occurrence and degree of agitation of the mind that the subject shows or says that he experiences, and the occurrence and degree of measurable changes in the body.

When Dr. Ackner and I began a combined study of some physiological variables during alertness, drowsiness and sleep it was soon apparent that the questions we were trying to answer had in fact multiplied the number of problems to be faced. In our measurements of electroencephalographic, respiratory, vasomotor and dermo-electrical changes, the variability in patterns from one subject to another was very marked and often difficult to predict. There were common trends and marked individual differences but these did not appear to be clearly related to particular clinical features. Moreover, in some of our investigations the physiological changes we measured revealed no gross differences between patients and members of the staff (Ackner and Pampiglione, 1955, 1957).

The first reports of Dr. Shagass' work (1954) were therefore read with great interest. Utilizing electroencephalographic and clinical changes induced by barbiturates he described a method of obtaining a quantitative index of tension in various groups of patients. This contribution appeared of importance not only because an objective pharmacological test was introduced in the quantification of symptomatology and grouping of patients but also because Shagass suggested particular physiological substrata of emotions. Moreover, he indicated the possibility that "the sedation threshold" as he calls some implications of his test "may reflect some basic neurophysiological aspect of personality organization"; as "not only the order but also the direction of the sedation threshold differences agrees with Eysenck's data and theory on introversion-extroversion" (Shagass, 1956).

Previous work had shown that the administration of barbiturates in man may evoke fairly constant and therefore predictable changes in the activity of the brain as measured electrically, particularly in the frontal regions. In addition when barbiturates such as Sodium Amytal are slowly injected into a vein a number of clinically observable changes may follow, such as drowsiness, difficulty in articulation, appearance of nystagmus, diminution in the speed and accuracy of movements, and later sleep. In normal subjects as well as in patients I had been unable to find any close correlation between the beginning of any of these phenomena and the development of the EEG changes in response to the drug. In another investigation with Dr. B. Mandelbrote and Dr. P. Sainsbury I was unable to establish any clear relationship between the time of appearance of the fast activity in the EEG and motor relaxation as recorded by a diminution in the action potentials from the muscles of the forehead and neck.

In the early days of electroencephalography it had been suggested that the records of anxious patients contained a great deal of fast activity. This is not so if we consider patients examined when no sedative has been given for many days and when no muscle action potentials mask the EEG.

The present investigation was undertaken both to establish the validity of Shagass' test in our hands, and also to study, together with the EEG, other physiological variables such as those measured by finger plethysmography and chest pneumography, utilizing the same material and test procedure. From a pilot investigation a number of methodological problems arose. It was found that some patients were more apprehensive than others about the actual test and that the intravenous injection could not be carried out in several patients who had either inaccessible veins all the time or had marked venous constriction at the time of the test. Some patients were very restless with their arms and hands, increasing the difficulties of intravenous injection and of obtaining a reliable trace of the pulse volume waves from the finger.

Commonly when the doctor entered the room there was a change in the patient's respiratory pattern and an increase in the muscle action potentials on the EEG and a moderate vasoconstriction. When the needle was inserted further vasoconstriction was seen as well as a marked increase in muscle activity which completely masked the EEG. A few minutes later the vasoconstriction diminished and the muscle action potentials became less prominent. Each subject was therefore tested twice within a few days and on the first occasion no Sodium Amytal was injected. This precaution demonstrated the variability in the autonomic reactions between subjects to the stress of the test situation.

It should be emphasized that the sedation threshold is based, according to Shagass, upon the combined occurrence of two phenomena, namely a change in speech (slur) and a change in the EEG (alteration in the gradient of the barbiturate-induced fast activity). In order to diminish the subjective element in the evaluation of "slurring" we defined slur as a disturbance of articulation, disregarding hesitation, slowness, and changes in phonation. In addition, as already described, the intravenous injection of Sodium Amytal at the appropriate dilution for the patient's body weight continued until the patient became unresponsive even if one of us had the impression that slurring had occurred. Recently Thorpe and Barker (1957) demonstrated that 16 listeners were unable to agree regarding the onset of speech slurring in their seven patients examined with the technique described by Shagass. Our precaution of reassessing the patient's disturbance of articulation *a posteriori* by repeating several times the run of tape recorder enabled us to check how often our preliminary judgment of slurring had been erroneous. In fact the assessment of a definite slurring point was doubtful in at least a third of our cases and many subjects appeared to speak normally for a time after a single occurrence of slur.

From the EEG aspect the methodology was more complex than at first pointed out by Shagass. In fact the fast activity response to barbiturates from different regions of the brain does not have the same growth curve in all patients though usually best seen in the frontal regions. Three EEG channels from 4 scalp electrodes (mid-frontal, right upper frontal, vertex, and left Sylvian) in standard position showed a considerable variability in the amplitude growth curve in each subject on each area of the brain. In view of previous personal experience patients suspected of cerebrovascular disease or other organic cerebral lesions were excluded from our series as their EEG response to barbiturates may be even more variable.

In order not to bias our impressions I did not begin to work out the measurements of the fast activity until 50 records had been collected. The correlations between the EEG and the clinical data were made still later. The mean amplitude of the frontal barbiturate-induced fast activity (15–30 c/s) was calculated over a period of one second at regular intervals after each cubic centimetre of solution injected and a curve of the changes in the mean amplitude was built up. A special ruler had been designed by Shagass to count the waves and add up their amplitude. There is no difficulty in measuring the mean amplitude of the groups of waves with such a ruler but the measurement was very tedious and it may take up to two hours to plot the growth curve of one channel in each record. Moreover in 6 cases in which the count was repeated differences were common and often as large as 20%. This percentage of error may not appear very great to those working in the EEG field and is certainly not larger than the quantitative error of commercial wave analysers. Shagass (1954) compared his hand measurements with those of a wave analyser and found a close correlation between the two.

As a general trend the fast activity from the frontal regions is minimal at first but during the injection it tends to increase and eventually a maximum amplitude is reached. The curve obtained according to Shagass should be an S-shaped pharmacological curve, the final plateau being preceded by a fairly steep rise. The point at which the gradient changes is called by Shagass the "inflection point" and according to him the patient slurs within 80

seconds from this point. Such combination of events determines the "sedation threshold".

As previously described the intravenous injection in our study was not interrupted at the time of the "apparent" slurring, but was continued until the patient did not answer any longer. In this way the growth curve of the barbiturate-induced fast activity was not arbitrarily interrupted. It was found that although some of the curves obtained were S-shaped and slurring occurred near enough to the first inflexion, most of the other curves were complex with several inflexion points. In a few others the growth was slow but steady without definite inflexions until the patient was well asleep. Because of these various difficulties a definite sedation threshold as defined by Shagass could be determined in only a third of our cases. This determination was impossible in another third of the cases and appeared doubtful in the remaining third.

Our patients were divided into three groups according to the severity of their anxiety. There was no substantial difference in these three groups of patients in the amount of drug injected by the time the patient began to slur. Moreover the mean amount of drug necessary to render the patient verbally unresponsive was remarkably similar in each of the three groups suggesting that the epiphenomenon of anxiety does not bear recognizable relationship to the patient's resistance to a sedative of the kind employed. The amount of drug necessary to reach the maximum amplitude of induced fast activity was also similar in these three groups of patients. Where a "sedation threshold" could be determined there was no marked difference between patients with minimal anxiety and patients with severe anxiety.

In order to assess the relationship between the "sedation threshold" and the diagnostic categories studied by Shagass our patients were grouped as follows: (*a*) anxiety and neurotic depression; (*b*) obsessional states; (*c*) mixed neuroses; (*d*) endogenous depressions; (*e*) hysteria. The mean "sedation threshold" was found to be the same (6 mg./kg. body weight) both for the group of anxiety and neurotic depression and for the group of hysteria. This is in marked contrast with Shagass' findings and his theory of physio-pharmacological personality differences. The mean "sedation threshold" was slightly lower (5 mg./kg. b.w.) in the other three clinical groups. The amount of drug required to induce unresponsiveness was not substantially different for each of these diagnostic categories. There was no correlation between the sedation threshold and the time and amount of increase in the pulse volume waves in these groups, nor any constant correlation with the variations in pulse-rate.

When the injection of Sodium Amytal is continued at the same rate until the patient becomes unresponsive a single clear inflexion point in the curve of induced fast activity in the EEG is recognizable only in a limited number of cases. The slur therefore should be essential in deciding which of a number of inflexion points is to be used in determining the threshold. We cannot agree with Shagass that "slurring" roughly localizes the threshold while the EEG does it accurately.

It seems likely that a subjective judgment of "slurring" could unconsciously be influenced by a knowledge of the patient's emotional state (or diagnostic category) with the production of correlations not obtainable by more objective methods of investigation.

I wish to express my thanks to the Mental Health Research Fund for a personal grant in connexion with this investigation.

## REFERENCES

ACKNER, B., and PAMPIGLIONE, G. (1955) *Electroenceph. clin. Neurophysiol.*, **7**, 153.
——, —— (1957) *J. Neurol. Psychiat.*, **20**, 58.
PAMPIGLIONE, G. MANDELBROTE, B., and SAINSBURY, P. (1954) Unpublished material.
SHAGASS, C. (1954) *Electroenceph. clin. Neurophysiol.*, **6**, 221.
—— (1956) *Psychosom. Med.*, **18**, 410.
THORPE, J. G., and BARKER, J. C. (1957) *Arch. Neurol. Psychiat., Chicago*, **78**, 194.

**Dr Peter Sainsbury** (Chichester):

Experimental studies which relate mental events and visceral changes due to autonomic activity are plentiful, but observations on changes in the activity of the skeletal muscles have not been numerous. This is surprising as changes in heart-rate or of the pupil, for example, have a less manifest relation to man's mental state than have the agitated movements of his hands or the tension in his facial muscles; and because the psychomotor behaviour of patients —their tense posture, their gestures and other expressive movements—are something we observe and avail ourselves of daily in the clinical examination and assessment of them. These muscular responses are the most conspicuous somatic manifestation of a patient's mental, and particularly his emotional, state.

The skeletal muscles can contract in only two ways: isometrically, that is, when tone increases without alteration in length; and isotonically, when the muscle shortens without change of tone and movement ensues. Ways must be found, therefore, to measure both tone and movements independently.

### A. *The Measurement of Tonic Activity*

The patient is asked to lie down, relax and remain still. Bipolar surface electrodes are strapped over the muscles whose activity is to be sampled. The muscle potentials from any active motor units are amplified and fed to an oscilloscope and pen recorder to monitor the tracing. In a tense muscle the recorded tracing is even, continuously sustained, of relatively low amplitude and free from irregular bursts of higher amplitude activity produced by movements. This low amplitude activity may be due to reflex postural tone in the muscle, or it may arise centrally as when the individual is alerted or aroused emotionally. Next, the potentials are passed to an electronic integrator which operates a counter.

### B. *The Measurement of Movements*

A movement appears on the record as a burst of activity of relatively higher amplitude, because in movement many motor units are rapidly recruited; and this type of activity is often superimposed on the sustained activity of lower amplitude due to reflex tone. To measure the movements, then, it is necessary to eliminate the effect of the tonic activity on the integrator. We have done this by placing a valve in the integrator circuit, the bias on the grid of which can be varied so that only those signals of a pre-selected amplitude are passed and counted. By inspecting the pen recording, a setting can be chosen at which all the low-amplitude, tonic activity is cut off: the larger spikes of movement remain to be counted.

When the integration reaches a certain value it triggers a valve which re-sets the integrator and passes a pulse to a pen which marks the paper record. The frequency of the marks varies with the integral (the area under the curve representing the potential); or, in practical terms, with the amount of movement the subject is making.

The procedure we use when recording movement is to have the patient sitting close to a table of a height such that he tends to rest his arms upon it: an arrangement which facilitates gestural movements of the arms. Small silver electrodes are placed over the maximum convexity of the forearm extensors and very light leads are passed to the back of the chair. The patient's clothes are then pulled over the electrodes and wires so that they are invisible to him and apparently they are soon forgotten. With this arrangement a record of shoulder elbow, wrist and finger movements is obtained. Should the patient rest his arm in a position involving continuous muscle strain—the chin supported in the cupped hand, for example—the tonic activity is usually still of a relatively lower amplitude and so not counted.

The apparatus is made to respond to the differing levels of muscular activity present in different patients by adjusting on the integrator the gains and settings which determine the amplitude of signals which will be counted.

Mr. J. C. Shaw, our research physicist, designed and calibrated the apparatus I now use at Graylingwell. At the gain commonly used, 670 microvolts give a 5 mm. deflection, and there is a linear relation between voltage and the recorded deflection of the pen. Similarly, on calibrating the integrator, a linear relation is found between the number of counts and the amplitude of the EMG tracing in millimetres. This relationship holds when the integrator is set to respond to *all* signals, as when tone in the muscle is to be recorded; and when it is set to respond only to those above 1, 2 or 3 mm. when movement is under investigation.

Satisfactory data on the daily stability of the integrator was also obtained.

### A. *Findings on Muscle Tension*

Jacobson (1938) was the first to record the action potentials in the muscles and to show they varied in a predictable way with mental activity and especially with feelings of tension. Next Malmo and Shagass (1949) showed in one of a number of valuable papers that anxious patients, on painful stimulation, had more activity in their neck muscles than did controls; and that in those patients with head complaints, presumed to be muscular, the neck muscle activity was significantly higher than in those whose symptoms were of a cardiovascular kind. Wolff (1948) also recorded electromyograms from the scalp and back muscles of anxious patients with symptoms referred to these areas and found that the activity in the muscle varied with the intensity of the symptoms.

Muscular relaxation has been developed as an effective therapy in tense patients by Jacobson and by Garmany (1952). These observations prompted Gibson and me to study, by a controlled experiment, the relation between the symptoms complained of by anxious

patients and the activity in their muscles (Sainsbury and Gibson, 1954). In order to limit the experimental conditions to the simplest and so avoid subjecting the patient to a stress situation which cannot be evaluated reliably, we measured the muscle activity occurring in our subjects when they were relaxing on a bed in a position which avoided reflex postural tone in the muscles being investigated. The sustained activity recorded under these conditions we called "*muscle tension*" to differentiate it from the activity due to postural tone, and we considered it to have a central origin.

The patient's complaints of anxiety and tension were scored by means of an inventory. The items were largely derived from a survey undertaken by Dr. Gibson, in which 29 senior psychiatrists at the Maudsley Hospital were questioned about the clinical observations by which they ascribed "tension" to a patient. Their answers clearly suggested that it is the general appearance of muscular over-activity, as judged from facial expression, posture, and so on, in the anxious patient which the majority of clinicians refer to when they describe their patients as "tense".

The patient's feelings and symptoms of anxiety and tension scored on the inventory were related to the counts of muscle activity. Records were obtained from the frontalis muscle of 30 anxious patients, and of 26 healthy soldiers, the controls. The muscle activity of each subject was counted for two 7-minute periods while he relaxed on a bed with eyes closed.

We found:

(1) The product-moment correlation between the counts for the two periods of relaxation was 0·9: the test-retest reliability of the counts was therefore satisfactory.

(2) The counts from the frontalis of the patients were significantly higher than from the controls ($P>0{\cdot}001$).

(3) Patients whose scores for feeling tense and anxious were above the median had significantly higher counts in both frontalis *and* forearm extensor muscles than those patients whose scores were below the median.

(4) A significant concordance was found between the measures of tension in four distinct muscle groups, which suggests that the body musculature as a whole received an increased innervation in patients who are anxious. This view was supported by another observation: that tense patients who complained of tremulousness or of starting unduly, symptoms which might be ascribed to a general increased innervation of muscles, had significantly more muscle tension in *both* their forearm and frontalis muscles than did patients without these complaints.

(5) Anxious patients with the symptoms referred to a definite area, such as tightness at the back of the neck, or a band across the forehead, showed significantly more activity in the muscles of that area than did those patients without such muscular symptoms.

I have recently collected further data for the hypothesis that muscle tension is positively related to emotional disturbance by measuring the activity in muscles of depressed and anxious patients on admission and again on discharge from Graylingwell. A significant decrease at the 5% level has been found.

To summarize these observations on muscle tension: the physiological measurement of it correlates with patients' anxiety scores and particularly with those complaints which may be reasonably ascribed to generalized muscle activity; also that the muscle tension is greatest in the muscle area to which the symptom is referred.

### B. *Findings on Movement*

An increase of spontaneous bodily movements might similarly be expected to form part of the picture of emotional disturbance. In fact, many of the spontaneous movements we make are commonly referred to as "nervous habits" and as "expressive movements", thereby acknowledging their relation to mental processes.

There are two categories of expressive movements we have measured. First, gestures, which accompany speech and so assist in communication; and secondly, those comparatively meaningless, self-directed fidgetings which Krout (1935) calls "autistic gestures". Everyday instances of autistic gestures are: unnecessary tie-adjusting, nail-biting, or the restlessness of the agitated patient.

A brief description of some of our experiments on these movements follows.

1) The validity of the scores of movement obtained: the counts on the EMG correlated 0·6 with those obtained by time-sampling the movements directly observed.

2) This experiment was designed to study the reliability of the movement scores. The gestures of 16 patients at Graylingwell were measured while they were interviewed for ten minutes on two occasions, separated by at least twenty-four hours. In these sessions the interviewer took the role of an interested listener, his only contribution being to encourage the patient to continue. The scores for movement during the two interviews correlated highly ($r=0{\cdot}87$). Another 21 patients sat *alone* for ten minutes on two different days. The product-moment correlation for their autistic gestures' scores was 0·76. These figures, in

addition to establishing the reliability, also suggest that the level of gestural activity is a characteristic attribute of the personality. I sought confirmation of this by correlating the movement scores made by these patients, while filling up a questionnaire, when alone, and while being interviewed. The concordance between the movements made in these three situations was significant at the 1% level.

(3) To test the hypothesis that emotional disturbance is accompanied by increased psychomotor activity: (i) The autistic gestures of 10 patients selected for leucotomy at the Maudsley and of 15 healthy controls, were counted by the EMG. The subjects in both groups were left sitting alone in a room for two periods of ten minutes each, on two separate occasions. The patients' mean movement score was significantly greater than the controls' ($P > 0{\cdot}025$).

The 10 *patients* were re-examined three months following their leucotomies. In the 8 patients in whom the operation effected an improvement in anxiety, tension and depression, there was a significant decrease of both gesture during interview and of autistic gesture while alone. Changes in the patients' gestures were measurable, therefore, and were related to changes in their emotional state (Sainsbury, 1954).

(ii) I have recently correlated the movements made by 21 patients sitting alone (their autistic gestures) and their ratings on an anxiety scale ($r = 0{\cdot}76$); and patients diagnosed as depressive or agitated depressive made significantly fewer movements than those in whom anxiety was the predominant feature.

(4) I aimed in another experiment to relate the amount of gesture to the content of a psychiatric interview planned to include topics of a kind likely and unlikely to disturb the patient.

The interview was recorded on tape. The patient also wore a throat microphone and this was fed to a pen which marked the electromyogram and integrator record when he was speaking. In this way we were subsequently able to synchronize the content of the interview on the tape with the movement scored by the pen recorder.

12 patients were given 16 interviews. The mean movement score for the half-minute intervals in which the topics discussed with the patient were those predicted as disturbing to him, were compared with the mean score during intervals in which his feelings were unlikely to have been disturbed. In all the interviews there was more gesture in the periods when disturbing topics were introduced: this increase was significant in 14 of them.

In three interviews every utterance of the patients was *independently* rated for the disturbance of affect manifested and the ratio of movements to words was scored for each utterance. It was found that the more affectively charged the utterance, the greater was the amount of gesture.

Finally, 4 patients were interviewed on a second occasion and it was found that those topics which had been accompanied by most gestures in the first interview were also those with most gesture in the second (Sainsbury, 1955).

Changes in the innervation of the voluntary muscles have, therefore, been found with emotion and they seem to be as much part of the physiology of emotion as are the changes in visceral innervation. In the last experiment, for example, the heart-rate was recorded concurrently with the gestures and was also found to increase with the disturbing topics. Evidence is accumulating that the hypothalamus and mid-brain mediate changes in the voluntary as well as in the autonomic pathways with emotional arousal or, indeed, with arousal of a less urgent kind such as when the individual simply attends to his surroundings.

The central discharge to muscles in these circumstances can be demonstrated as changes in spontaneous movement and in muscle tension. The former are evident clinically as restlessness, or as an increase in gesture; the latter as a stiff posture, or furrowed brow. Subjectively this increased muscular innervation is described and experienced, we found, as irritability, feeling on edge, as tightness or even pain in the muscle, or simply as feeling "tense" (a term 79% of our patients used to mean that they were unable to relax muscularly).

It would be consistent with our findings, with the reports of the majority of our patients, and with what we found to be the practice of the majority of psychiatrists, if the term "tension" were limited to the muscular manifestations of the emotion.

## REFERENCES


GARMANY, G. (1952) Muscle Relaxation. London.

JACOBSON, E. (1938) Progressive Relaxation. 2nd edit. Chicago.

KROUT, M. H. (1935) *Psychol. Monogr.*, **46**, No. 208.

MALMO, R. B., and SHAGASS, C. (1949) *Psychosom. Med.*, **11**, 9, 25.

SAINSBURY, P. (1954) *J. ment. Sci.*, **100**, 732.

—— (1955) *Psychosom. Med.*, **17**, 458.

——, and GIBSON, J. G. (1954) *J. Neurol. Psychiat.*, **17**, 216.

WOLFF, H. G. (1948) Headache. New York.

Dr. **Denis Hill** (London) said that while the recognition of stress was a relatively easy clinical task and its treatment, especially by the new tranquillizing drugs, had made some progress, its measurement had always proved a baffling problem. There were different ideas about the nature of emotional tension. Could it be described only as an over-readiness to respond to meaningful stimuli, or is it an enduring state of activity within the nervous system, or perhaps a biochemical lesion? If the first of these was correct then all evidence of tension should disappear in sleep when the meaning of stimuli ceases; on the other hand if the second alternative was correct then even in deep sleep there might be some positive evidence of abnormal functions which could be related to the state called "tension". Clinical evidence concerning the sleep of tense patients favours the second hypothesis. The problem of understanding how emotional tension could persist as an organization within the nervous system as an enduring state is a problem common to all those issues concerning the relationship between neuronal and mental activity. To solve one such problem may be to solve all. For example, if we understood how memories were retained within the nervous system through waking and sleeping life, through the violent disturbances of concussion and E.C.T. and many other circumstances which profoundly alter cerebral activity, we might well understand how an emotional state such as tension could persist.

From the physiological point of view the probable mechanisms concerned with tension are largely inaccessible; only the effects are discernible. The speakers had shown how studies at two ends of the system could help in such measurement. Recent studies by Drs. Ackner and Pampiglione had shown that it was the same nervous mechanism which caused physiological arousal of the cortex and changes in the calibre of peripheral vessels. No doubt this applied too, as Dr. Sainsbury suggested, to the changes in muscular tonicity. It seemed highly probable that the mechanism involved was the much-discussed mid-brain reticular system.

Shagass' idea of a sedation threshold seemed at first sight a fairly simple thing. From his early work he had suggested that the sedation threshold is a constant for the individual, perhaps a constitutional character. Shagass' most recent paper, however, and the new evidence of Drs. Ackner and Pampiglione made it clear that the sedation threshold is not a constant for the individual, but varies with his degree of manifest tension and anxiety and with illness, and also can be altered when the techniques by which the threshold is measured are altered. Moreover it is for some patients a measurement which cannot be made because there is no clear end-point or because the two measurable factors—fast rhythm facilitation and slurring of speech—dissociate in some patients. It would seem that the sedation threshold does not vary directly with what is called clinically emotional tension, or rather that the method may point the way to differentiating various types of tension. The results of these studies on cortical function contrast strongly with those made on peripheral structures, described by Dr. Sainsbury and by Dr. Ackner. The ingenious sampling devices developed by Dr. Sainsbury enable him to observe a part of muscular functions—and he can vary his sampling mechanisms to observe any part of these functions which he wishes. Moreover this can be done with minimal stimulation or threat to the patient. The correlations with clinical tension which emerge seem quite clear, just as do those relating to vasomotor tonus which Dr. Ackner had described. These methods seem to hold great promise for future work.

The results on the sedation threshold, inconsistent with those of Shagass, which Drs. Ackner and Pampiglione had described, are not surprising. In the case of peripheral vasomotor tonus and in the case of muscular tonicity it might be surmised that the mechanisms by which the excitability of spinal motor neurones are influenced by the mid-brain reticular system are relatively simple, involving few neuronal pathways—simple that is, in comparison with the mechanisms involved when one thought of the action of the mid-brain system in the opposite direction, on the cerebral cortex.

Shagass himself evoked the idea of another variable, "impairment of ego functions", to explain the differences in threshold between anxious neurotics and anxious psychotics. It is surprising that these results place hysterics, psychotic agitated depressions and organic dementias in the same functional category.

There was little doubt that studies such as they had heard about held great promise for the future. The benefit to clinical practice and to therapeutics in psychiatry would be enormous if reliable measurement of emotional tension could be achieved. The research worker in this field is, however, always limited by the fact that the more he wishes to observe, the more he interferes with what he observes. The patient attached to a laboratory full of apparatus is liable to resemble the traveller prepared for a journey into outer space and experiences no doubt some of the apprehension which such travellers will experience. One could only hope that the ingenuity and resourcefulness which the speakers had obviously brought to bear on their work would continue to open the way for them in the future.

**Dr. Murdo Mackenzie** (London):

The opening papers have stressed the importance of measurement in the investigation of emotional tension: and it seems prudent to emphasize the need for uniformity in the use of words to denote the several entities which are being examined.

The word "depression" has been cited, but in such different contexts as to suggest a lack of precision in the employment of the term. The diagnosis covers, *inter alia*, simple depression, reactive depression, endogenous depression and agitated depression.

The word, in ordinary language, is used in two disparate ways: one connotes lowering, as for instance, in a barometer to indicate atmospheric change; the other depicts reduction in vigour, as for example, a recession in the trade cycle. The variant of meaning is rendered clear, in each instance, by the object to which it refers.

Depressive states, as observed in the clinic or consulting room, reveal similar differentiation. One patient affirms "I am all in and can face no more strain"; another declaims "It has been the same all my life. I may appear, in a sort of way, successful; but, *au fond*, I am bogus and know it".

The first averment refers, manifestly, to a sense of loss of vitality; and the second to a lowering or denigration of the individual personality, by a psychological device. It would be of assistance, then, in the delineation of states of emotional tension if the distinctive uses of the word were preserved.

The term "personality" has been quoted in the discussion; and it, too, suffers from a general lack of consistency in application. Dr. Leopold Bellak, for instance (1956), writes of the "psychoanalytic theory of personality". Dr. Margaret Mead, on the other hand, in the same series (1956), employs "personality" to denote ". . . the total pattern of the individual's behaviour . . ." The other essays show a corresponding diversity of approach.

Personality, in everyday language, suggests the notion of a distinctive individual trait; and an interesting feature of great personalities is the way they show enduring contrast in presentation. Sir Winston Churchill, for instance, came to one of his peak points in oratory in the speech on "the beaches of Britain": in this the emphasis is on an accentuation of the significance of the "here and now". President Franklin Delano Roosevelt, on the other hand, in a similar situation, created the fireside chat on the wireless; in this the emphasis in presentation resides in a diminution of the significance of the "here and now".

If personality be defined as presentation with individual contrast, the concept might be used to further the observations on muscular contraction, in individuals under conditions of strain, described in one of the opening papers. Some patients asseverate that they, invariably, respond to stress by a manifest gesture: others affirm that they, automatically, assume the "poker face". The duality might be found to correspond with differing methods of presentation in personality contrast.

Precision in the use of terms can, at all events, only assist in promoting accuracy in the quest for "physiological measurements of 'emotional tension' ".

## REFERENCES

BELLAK, L. (1956) In: Psychology of Personality. Editor: J. L. McCary. New York; p. 1.
MEAD, M. (1956) In: Psychology of Personality. Editor: J. L. McCary. New York; p. 201.

# Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

[*October* 9, 1957]

## DISCUSSION ON NERVE PRESSURE SYNDROMES

**Dr. I. Meanock** (Reading):

*The Problem of Paræsthesiæ in the Upper Limb*

I shall discuss only those conditions in which it is believed that pressure on a nerve is a causative factor in the production of paræsthesia. Between 8% and 10% of patients attending my out-patient clinics complain of tingling in some part of the upper limb.

In the past, *cervical rib syndrome* has been invoked as one of the commonest causes of paræsthesiæ in the upper limb. The number of alternative labels given to this syndrome, such as costo-clavicular compression, rudimentary first rib, scalenus anticus syndrome and acroparæsthesiæ, indicate several of the known factors in the production of this symptom complex.

In cervical rib syndrome a variable combination of anatomical, physiological and pathological features are involved in the production of symptoms; hence, whatever synonym is used for the condition, it is never the sole factor concerned.

The tingling in the digits, so frequently associated with recurrent coldness and cyanosis, results from the vascular component, as does the pain in the deep structures of the forearm and hand, also the intermittent obliteration of the radial pulse. Characteristically these findings are reproduced by traction on the dependent limb and the deep pain is increased and cramplike when the limb is in use for prolonged periods. The tingling is accompanied by numbness in the digits and often objective changes in cutaneous sensibility. The true nervous symptoms of rib pressure include muscular wasting and sensory loss in which the distribution is quite definite. It may involve sensory changes on the thumb and radial side of the hand, with weakness of opponens and abductor pollicis, or in other cases pain and sensory loss on the ulnar aspect of the hand with ulnar-type motor changes involving the hypothenar muscles, interossei and adductors of the thumb.

Wilson (1940) has suggested that the probable explanation for the sparing of flexor pollicis brevis is that its root supply is from C.8, whereas abductor and opponens pollicis are supplied by the C.7 root.

Cervical rib syndrome is but one of the conditions in which pain and paræsthesiæ are most distressing at night. This exaggeration of pain at night is thought by Walshe (1951) to be due to the increased pressure on the nerves at the outer border of the first rib in the supine position, when the shoulders tend to fall backwards. It is at this point on the first rib that the fibres passing to the ulnar nerve and the inner head of the median nerve are gathered. Behind the inner cord of the plexus is the nerve to serratus anterior. If we accept this outer border of the first rib as the likely pressure point, it offers an explanation for the occasional weakness of serratus anterior in the syndrome of cervical rib.

As with some other causes of paræsthesiæ in the hand, cervical rib syndrome is common in middle-aged women. Sagging of the shoulders from fatigue, debility or unaccustomed use of the hands may be operative factors. That this is likely is borne out by the fact that rest

is the most effective form of treatment in all but the most severe cases, when surgery may be necessary. Rest to the affected limb is most easily achieved by wearing a sling, care being taken to ensure that the weight of the limb is carried on the unaffected side. Whether rest is accompanied by the common practice of instructing the patient in shoulder elevating exercises or not appears to be immaterial.

*Cervical spondylosis* is perhaps a major cause of pain in the upper limb. It is regrettable that this essentially radiological entity has come to be applied to a clinical syndrome. Although cervical spondylosis is probably the commonest cause of disease of the spinal cord over the age of 50, it should be remembered that some 65% of the population over this age have the characteristic X-ray appearance (Bradshaw, 1957) and hence it should be regarded as a part of senescence and usually symptomless. The most significant radiological signs are loss of normal cervical lordosis and restriction of movement, as demonstrated with films in flexion and extension and the presence of osteophytosis. Narrowing of a disc space is naturally of importance but may not be associated with posterior osteophyte formation. Such an osteophyte may be present, however, without any apparent disc narrowing.

Protrusion of the annulus fibrosus is regarded by Brain as being the more important disc lesion in the cervical region and it is to this condition and the associated changes in the adjacent vertebral margins that the term "cervical spondylosis" is applied.

The ætiology is complex and necessarily somewhat hypothetical. External trauma is thought to play but a small part: less than 25% of a recent series gave a history of an important head injury.

The frequent association of disc degeneration at several levels of the spine suggests that it may be related to the metabolic process of ageing. Local wear and tear must play a part for it has been noted that the excessive movement in joints adjacent to a congenital lesion, such as fusion of vertebral bodies, results in disc degeneration in these excessively mobile joints.

In patients with spondylitic narrowing of the disc space there is considerable variation in the direction of the lower cervical roots; rarely do they run horizontally, but rather upwards and downwards. This course necessarily brings them into contact with the lower or upper margins of the intervertebral foramen and its adjacent osteophytes.

That the nerve is compressed against the posterior wall of the intervertebral foramen by a bony spur is sometimes evident at operation, but many cases at operation do not show either angulation or compression. It is in these cases that the work of Frykholm (1951) appears to be especially important, for he has demonstrated the fibrosis of the root sleeve following stretching, angulation or compression. The result of this fibrosis is to fix and further angulate the nerve root so that movements of the neck stretch the nerve and produce symptoms.

Paræsthesiæ are a frequent complaint in cervical spondylosis and when caused by cervical myelopathy, as opposed to root irritation, cord involvement is evident because of the predominant findings in the lower limb of pyramidal tract involvement.

The onset of radicular symptoms in cervical spondylosis is usually insidious, with burning or tingling sensations sometimes accompanied by pain radiating down the upper limb into the digits. It is particularly troublesome at night. If the onset is acute, it resembles disc protrusion but more often it is chronic and relapsing, or alternatively remaining as a persistent discomfort in neck and arm. Since a single spinal posterior root innervates not only its corresponding segmental cutaneous area or dermatome, but also muscles, joints, ligaments and even viscera remote from the corresponding dermatome, pain caused by irritation of a root may radiate widely to the front and back of the chest. The pain is felt as a deep ache in the proximal muscles with periodic attacks of pain radiating more peripherally into the fingers or up into the neck.

Motor symptoms are unusual but occasionally predominate and may be so rapid in onset as to cause confusion with anterior poliomyelitis.

Slight muscular weakness and hypotonia in muscles innervated by the affected spinal nerve are not uncommon, and the tendon reflexes mediated by these muscles may be diminished. Hyper- or hypo-æsthesia within the dermatome of the affected nerve and weakness and tenderness in corresponding muscles are frequent findings. Neck movement may be surprisingly good, lateral flexion being the most severely affected. Manual pressure on the vertex increases the discomfort and upward traction on the chin often relieves it.

The features of the older clinical accounts of brachial neuritis, in which pain and paræsthesiæ spread throughout the arm to the fingers, with muscular wasting and diffuse sensory loss, may occur in cervical spondylosis, even when on X-ray only one or two disc spaces appear to be affected.

Acroparæsthesia, being defined as unpleasant tingling affecting some or all of the digits developing at night, is so common in cervical spondylosis that its presence justifies X-ray of the cervical spine. It is, however, a common symptom of cervical rib, the so-called

"housewives' neuropathy", and is invariably present in median carpal tunnel compression.

The condition of "frozen shoulder", particularly in the older age groups, is often the result of pain referral to the shoulder from root irritation. The importance of this lies in the approach to treatment, which must be directed in the first instance to the spine rather than to the shoulder.

With the increasing popularity of the diagnosis "cervical spondylosis", and the very varied neurological syndromes found in association with it, there is a very real danger that unconnected neurological disorders will be overlooked.

In the elderly patient, for instance, tingling in the finger tips with slight unsteadiness in walking can easily be attributed to cervical spondylosis if subacute combined degeneration of the cord has not been excluded. Syringomyelia has similarly been missed in the presence of a radiological finding of cervical spondylosis. The reverse situation is still encountered where after many years with a diagnosis of disseminated sclerosis a patient at last finds hope of alleviation in treatment directed to the cervical spine.

Similarly, there is the case of cervical spondylosis masquerading as motor neurone disease, where even if a brisk jaw-jerk has been recorded, the presence of impairment of vibration sense in the lower limbs should be sufficient to rule out what is purely a motor disease.

There is wide scope for diagnostic errors in elderly patients with spondylitic changes, in the pains of cardiac ischæmia, apical lung tumours or periarthritis of the shoulder-joint.

The association of paræsthesiæ of the upper limb with emotional disturbances seems to be too frequent to be a chance one. While it is true that an emotional and tense patient may magnify minor physical discomfort in the arms and neck, another explanation seems equally feasible.

It is recognized that the increased muscle tone produced by such a factor as cold, may, in spondylitic subjects, provoke symptoms. Is it not possible then that the tense, emotional and agitated patient who shows increased muscle tone by the presence of exaggerated reflexes and tremor, may not similarly provoke symptoms? It is certainly true that some of the most stubborn cases whose symptoms have resisted many months of treatment by physical means have been improved, even to the extent of losing unequivocal physical signs, on the administration of tranquillizing agents.

The lesson to be remembered, therefore, is that the diagnosis of cervical spondylitic radiculopathy must be based on the history and physical signs and not on the demonstration of radiological changes.

Mention must be made of the concept put forward by Russell (1956) that the symptoms of neuropathy in cervical spondylosis are largely due to changes in the nerve sheaths. He believes that the problem has been oversimplified by the adoption of recent views on cervical spondylosis. The tenderness of nerve trunks, so evident by tapping or stretching the nerve, depends on an abnormal state, not of the traversing nerve fibres but of the nerve sheath. There is pathological evidence of the irritating effect of spondylitic lesions on adjacent nerve sheaths.

Russell infers that pressure on a nerve or nerve root is not in itself the cause of painful neuropathy, but rather that the pain depends upon the production of a neuritis in which the important changes are in the nerve sheath and that the treatment of the neuritis is more important than attempts to treat the cervical spondylosis directly.

There appears to be a condition somewhat intermediate between cervical rib and spondylosis in which some features of both conditions may be present. I refer to housewives' neuropathy in which pain is the salient and often the only symptom. This pain is felt mainly in the proximal part of the limb and is easily reproduced by direct pressure above the clavicle. Manœuvres which compress or stretch the nerves in the shoulder region, such as resisted abduction of the upper arm, pulling on the arm and forceful external rotation of the shoulder, reproduce the pain.

Hypoæsthesia of the fingers in a glove distribution but without any reflex or muscle changes is common.

Women with drooping shoulders appear to be very prone to this condition, particularly if they undertake unaccustomed or prolonged periods of work with the hands. This intermediate group of patients is the largest but fortunately it is very amenable to treatment. Occasionally the severe case has to be admitted to hospital in order to obtain complete rest for perhaps two weeks but most cases can be satisfactorily treated as out-patients. The arm is rested in a sling while the pain is severe or continuous. After a few days, when the acute pain has subsided, a series of shoulder exercises is started and the sling is slowly discarded over a period of three to four weeks.

The exercises should be continued for several months, or relapses will occur.

One type of paræsthesiæ in the upper limb in which treatment is dramatic is *median nerve compression* where this occurs in the carpal tunnel.

Of the two groups of patients the less common type is that in which underlying pathology can be determined, such as old fracture of wrist with or without secondary degenerative change, or in whom osteoarthritis is present, or as part of rheumatoid disease—in this connexion it is worth mentioning that on follow-up I have found that carpal tunnel compression was the presenting lesion in five cases of rheumatoid arthritis; the more frequently occurring group typically consists of middle-aged women in whom the disorder, although primarily occurring in the dominant hand, later involves both hands in more than half of the cases.

The initial symptoms are always sensory and consist of a burning and tingling in the fingers, mainly at night, frequently waking the patient. The most severe nocturnal symptoms arise some hours after strenuous use of the hands. Knitting and sewing are particularly troublesome in this respect.

An aching sensation is felt deep in the wrist and may spread up into forearm and even to arm and shoulder region. Later, blunting of sensation occurs which interferes with the handling of small objects. This hypoæsthesia in the distribution of the median nerve is found in the majority of cases.

Objective sensory loss is never proximal to the wrist and palmar sensation is not usually affected because this cutaneous branch of the median nerve leaves the main trunk above and therefore lies anterior to the carpal ligament. Wasting of the outer half of the thenar eminence is more evident if the thumbs are viewed in profile, when weakness of abductor brevis and opponens pollicis is often conspicuous. The motor change, such as the weak opposition of the thumb, adds to the clumsiness in handling, due to sensory disturbance.

Typically, the fifth finger is spared but the fact that it is sometimes involved requires at least the conception of segmental overlapping to explain it, as does the frequent presence of pain in the forearm.

Ischæmia of the tendons is a likely cause for the occurrence of stiffness of the fingers when the patient awakens.

Several simple tests often help to establish the diagnosis. The tourniquet test (Gilliatt and Wilson, 1953) of ischæmic paræsthesiæ and sensory fading, after obliteration of the radial pulse, is valuable. It seems very probable that a similar ischæmic compression of the nerve takes place during sleep, when œdema of the tissues is maximal and the patient may lie on the arm.

The normal wrist, if excessively flexed, can give rise to paræsthesiæ, but if these occur within 60 seconds of flexion, it is thought to be diagnostic.

Brain (1948) has shown that pressure within the carpal tunnel is greatest in extension. This affords some explanation of the occurrence of symptoms in women whose tasks, as opposed to those of men, require extension—for example, scrubbing or polishing. Light percussion of the median nerve at the wrist will reproduce paræsthesiæ in 80% of patients. The treatment should be directed to the cause as far as it has been determined. Rest is necessarily a vital part of the management of all cases, and wrist splintage in the neutral position is effective in the majority. The immediate response to splinting the wrist is used by some as a therapeutic test. I have found hydrocortisone injection into the region of the carpal tunnel valuable in cases of recent onset.

Section of the transverse ligament, preferably by open operation, is indicated in cases resistant to simpler treatments. If muscular weakness has been present for more than one year, the results of operation are poor. In a few cases, no obvious cause is found at operation and yet relief is obtained, though sometimes only temporarily. I now have two cases under my care where operation was apparently successful, but after periods of five and thirteen months symptoms have recurred.

I believe open operation to be more successful than the blind operation where some fibres of ligament may be left intact.

Fluid retention has been mentioned as a possible factor because of the occurrence of this syndrome in pregnancy and obese subjects. On the basis of a rather flimsy hypothesis, I have used weight reduction and Diamox in addition to rest in obese subjects, and it is my clinical impression that they improve more rapidly than their asthenic sisters.

The differentiation of the main causes of paræsthesiæ in the hands is not always immediately obvious. In cervical spondylosis, although pain and paræsthesiæ are often present in the digits, they are equally found in other parts of the limb from the shoulder down, and may include the neck and chest. Sensory loss, if present, is not localized to the distribution of the median nerve, and wasting is not confined to the outer half of the thenar eminence. In fact, wasting of the hand is rare in cervical spondylosis unless there is damage to the cord at the cervical level, when signs of involvement of the sensory and motor tracts are present. Diminished tendon-jerks, particularly the triceps, are frequent in cervical spondylosis, but never found in carpal tunnel syndrome.

If costo-clavicular compression of the brachial plexus causes sensory symptoms only,

these are not limited to distribution of the median nerve. If, on the other hand, localized pressure on the inner cord gives rise to muscular wasting, involving muscles of the thenar eminence, the accompanying sensory loss and dysæsthesia are not within the median nerve distribution, but correspond to the 8th cervical and 1st dorsal dermatomes.

The condition of tennis elbow may give rise to confusion since pain and paræsthesiæ are not infrequently found in the forearm, mainly, however, on the extensor surface of the forearm and the dorsal surface of the fingers. The diagnosis can clearly be established when the symptoms are reproduced by resisted extension of the wrist.

Ulnar nerve compression, giving rise to paræsthesiæ, sometimes occurs in lesions of the elbow-joints. It is often insidious in onset and may follow years after an injury to the joint, particularly if this has resulted in a valgus deformity of the joint. Osteophytic outgrowths in arthritis of the joint may damage the nerve, as may a Charcot elbow.

Occasionally repeated minor trauma, in occupations involving constant and forceful flexion of the elbow, may give rise to a pressure neuritis with a palpable thickening of the nerve behind the internal condyle of the humerus. The earliest symptoms are pain and paræsthesiæ in the fifth finger and ulnar border of the palm; the motor changes are rarely complete.

Appropriate operation will free the nerve from pressure and sensory symptoms rapidly improve, but recovery of voluntary power is necessarily slow. Splintage is sometimes indicated to prevent a claw hand developing. It is customary to use a splint to produce flexion of metacarpophalangeal joints and extension of interphalangeal joints.

## REFERENCES


BRADSHAW, P. (1957) *Quart. J. Med.*, **26,** 177.
BRAIN, W. R. (1948) *Proc. R. Soc. Med.*, **41,** 509.
FRYKHOLM, R. (1951) *Acta chir. scand.*, **101,** 457.
GILLIATT, R. W., and WILSON, T. G. (1953) *Lancet*, ii, 595.
RUSSELL, W. R. (1956) *Proc. R. Soc. Med.*, **49,** 198.
WALSHE, F. M. R. (1951) Modern Trends in Neurology. London.
WILSON, S. A. K. (1940) Neurology. London; Vol. 2.


**Dr. R. W. Gilliatt** (London):

*New Methods of Investigating Peripheral Nerve Lesions*

Our interest in these problems at the Middlesex Hospital arose from a chance observation which was made there in 1950.

In November of that year an elderly man was admitted to the neurological ward under the care of Dr. M. Kremer with symptoms which we should now recognize as being due to a carpal tunnel syndrome, but which we then labelled acroparæsthesiæ without any clear idea as to their cause. The patient complained of intolerable burning pain in one arm, accompanied by tingling in the hand and fingers, these having been present for about three months, occurring in attacks which were at first mainly nocturnal. His pain and tingling later increased during the day so that by the time the patient was admitted to hospital he was unable to work and was suffering severely from loss of sleep. The patient himself had noticed that his symptoms were greatly affected by the position of his arm; for example, pain could be precipitated by holding up a book or newspaper and it could be abolished by lowering his hand and allowing it to hang down over the edge of the bed. Examination in hospital revealed no abnormal physical signs in the nervous system to account for his symptoms, but the effects of posture which he described could be reproduced in the ward. When the left arm was raised voluntarily, or when it was held passively above his head, pain in the limb became unbearable within a few minutes and lessened when the limb was lowered. For interest, a blood pressure cuff was inflated round the upraised arm to occlude the arterial supply, and we found that when this was done severe pain persisted after the arm was lowered for as long as the cuff remained inflated. Later we found that arterial arrest by itself would produce intolerable pain regardless of the posture of the limb. With rest in bed the patient's symptoms improved and after two weeks in hospital he was discharged. No definite cause for his acroparæsthesiæ had been found and although the experimental findings were of some interest they were difficult to interpret in the absence of a firm diagnosis. They remained an isolated set of observations and for two years none of us thought more about them. Soon after leaving hospital, however, the patient's symptoms recurred and during the following year motor and sensory changes developed which established the diagnosis of median nerve compression in the carpal tunnel. Eighteen months after his first admission to hospital the flexor retinaculum was divided surgically with complete relief of symptoms.

At this time the experiments that we had done with the blood-pressure cuff in 1950 were recalled and a tentative explanation suggested. Elevation of the arm above the head and obstruction of the circulation with a pneumatic cuff are both procedures which cause ischæmia of distal structures, and in this patient they had both resulted in severe exacerbation of his

paræsthesiæ and pain. It seemed likely that the damaged median nerve at the wrist had become abnormally sensitive to changes in its blood supply and that the patient's spontaneous attacks of pain might have a similar basis. Accordingly we began to use cuffs to investigate more patients with carpal tunnel syndromes and to compare them with patients with other peripheral nerve and root lesions (Gilliatt and Wilson, 1954) and also with patients with spinal and cerebral lesions affecting the hand (Gilliatt, 1955).

The information that may be obtained by a tourniquet test can be summarized as follows. In the first place, patients with carpal tunnel syndromes may not be able to tolerate arrest of the circulation by a cuff around the arm because it produces severe pain in the hand which they recognize as similar to that of their spontaneous attacks. Normal people do not get severe pain in the arm due to a pneumatic tourniquet provided that they do not contract muscles and produce ischæmic pain, but a patient with a carpal tunnel syndrome may get something very closely resembling his spontaneous symptoms, and on several occasions we have seen patients hanging their arm over the edge of the bed during a cuff test as if they were having a spontaneous attack.

For severe pain to occur in the hand and arm as a result of circulatory arrest is the exception rather than the rule in patients with carpal tunnel syndromes, and in my own series of 100 tourniquet tests done in 1952 and 1953, pain of this sort only occurred in about one case in every six. When this pain does occur it seems to be due to the direct effect of ischæmia on the median nerve at the wrist, and it will persist until that particular segment of nerve receives further blood supply. In this respect it does not really matter whether the cuff is high in the arm or in the forearm or even just above the wrist itself.

The second abnormality which may be shown by patients with carpal tunnel syndromes during circulatory arrest is tingling in the median-supplied fingers. Between a third and a quarter of my patients showed this sign which is a clear indication of a damaged median nerve; although most normal people experience some tingling in the hand during circulatory arrest it is never felt entirely or predominantly in the median fingers, the normal result being either a diffuse tingling throughout the hand or a sensation referred mainly to the ulnar fingers. In the carpal tunnel syndrome median tingling is, I think, mainly due to the effect of ischæmia on the damaged segment of nerve at the wrist and, like the pain, it does not seem to be abolished by altering the position of the cuff in the arm, provided the blood is not allowed to flow back to the region of damaged nerve.

The third thing that may happen during a cuff test is the appearance, within a few minutes, of sensory loss of a characteristic distribution or alternatively exaggeration of sensory loss already present in the hand. It is unusual for normal people to develop any definite sensory changes in the fingers within ten minutes of the inflation of a pneumatic tourniquet around the arm, but in our patients with carpal tunnel syndromes the cuff produced changes within ten minutes in more than half. This last effect of the cuff is not quite like the two previous ones that I have described, as it may occur in any patient with a peripheral nerve lesion, regardless of whether it is a median nerve lesion at the wrist, an ulnar nerve lesion at the elbow, or a lesion in the thoracic inlet or even in the cervical root. In each case sensory loss of characteristic distribution appears or becomes more obvious during ischæmia in relation to sensation in the surrounding skin.

With regard to the practical value of these tests in diagnosis, I should say that the pneumatic tourniquet has a small but definite place in the investigation of the sort of patient under discussion. Its advantages as a test are that it is cheap and simple and that it may uncover physical signs which are not obvious on formal neurological examination. It has disadvantages in that it is time-consuming and may be unpleasant, so that patients require a lot of encouragement while it is going on. Its third disadvantage is the more fundamental one that it still requires the co-operation of the patient, as it uses a question-and-answer technique like an ordinary sensory examination. This is a very considerable disadvantage as it is particularly in the "poor witness" type of patient who gives unreliable replies to all questions that one wants an objective test, which this is not. In contrast, there are now electrical tests available which provide objective information about nerve function and which require no co-operation from the patient so that they can even be done on anæsthetized patients. From my own experience there is no doubt that I would rather have an electrical test than a cuff test in a difficult case because the electrical test by-passes this problem of the unco-operative or unreliable sensory witness, but I add the rider that when and where the electrical equipment is not available there is still a place for simple tests with a pneumatic cuff.

The first electrical method that I am going to describe was introduced by Dawson and Scott in 1949. A brief electrical stimulus is applied to the median or ulnar nerve at the wrist which causes a synchronous volley of impulses to pass up the nerve trunk. As the volley passes up the arm its action potential is picked up by surface electrodes placed over the course of the nerve just above the elbow. This action potential is amplified in the usual way,

displayed on a cathode-ray tube and photographed. In this case the afferent volley contains antidromic impulses in motor fibres as well as sensory impulses; in order to obtain a purely sensory volley, Dawson (1956) devised a method of stimulating the digital nerves themselves with ring electrodes wrapped round the fingers, the afferent volley being recorded as before by surface electrodes placed over the median or ulnar nerve trunk in the arm.

In 1956 Sears and I began to use Dawson's technique to examine patients, and in order to produce a standardized clinical test we decided to restrict ourselves to stimulation of the fingers with recording of the afferent volley at the wrist; to test the median nerve we applied our shocks to the index finger and for the ulnar nerve we stimulated the little finger. With this simplified technique, we were pleased to find we could record sensory action potentials from normal median and ulnar nerves without difficulty and in a large number of controls there was no case in which the potentials failed inexplicably to appear. We then transferred our attention to patients with peripheral nerve lesions affecting the hands, and often found that the sensory action potentials were absent or delayed and reduced in size (Gilliatt and Sears, 1958).

We now use this sensory conduction test routinely in patients with sensory disturbance affecting the upper limb. To my mind it has three main advantages: in the first place it will sometimes provide evidence of abnormality when ordinary clinical examination fails to reveal it. This obviously depends on how carefully the clinical examination is done, but we have records of some patients where the most elaborate sensory tests with compass points and nylon hairs have failed to show sensory loss, yet where electrical studies have shown abnormal sensory conduction. The second advantage of the electrical test is that it provides objective evidence of abnormal function. The patient does not have to co-operate except that he has to lie still; when he has refused to lie still we have given him intravenous Sodium Amytal and still obtained our records. The third advantage of the method is that it provides information which helps to localize the level of a lesion causing sensory loss.

For this purpose we always use our sensory tests in conjunction with measurement of motor nerve conduction velocity. Motor nerve conduction studies in these cases were first carried out in this country by Simpson (1956) and his technique is very simple. It involves stimulating a motor nerve trunk at various levels in the arm, a recording needle being placed in the appropriate muscle so that the time from the stimulus to the earliest electrical sign of a muscle response can be measured. Simpson's technique, therefore, measures the conduction time in the fastest surviving motor nerve fibre supplying a particular muscle and, by stimulating at more than one level in the arm, conduction rates can be compared in different parts of the same nerve.

Let me conclude by summarizing the characteristic electrical features of peripheral nerve lesions at different levels in the arm.

(1) Lesions of the deep branch of the ulnar nerve in the palm: a long delay in motor nerve conduction between the wrist and the affected muscles is usually present with relatively normal conduction velocity in the ulnar nerve above the wrist. The hypothenar muscles are nearly always spared and show normal motor nerve conduction throughout. The sensory action potential from the little finger is usually quite normal.

(2) Median nerve lesions at the wrist: a motor delay between the wrist and thenar muscles is the typical finding: it has been present in just over half of our cases. The sensory action potential, recorded from the median nerve above the wrist when the index finger is stimulated, has been absent or else small and delayed in about two-thirds of our cases.

(3) Ulnar nerve lesions at the elbow: motor nerve conduction velocity is relatively normal in the upper arm, but is slow in the elbow region and perhaps below it. As Simpson originally suggested, the slowing is most obvious in the region of the elbow, but there is no doubt that in a proportion of these patients conduction remains slow throughout the forearm and hand right down to the muscle. The sensory action potential from the little finger may be reduced or absent at the wrist, but in mild cases a more clear-cut result is obtained by stimulating the ulnar nerve trunk at the wrist and recording above the elbow.

(4) Cervical rib syndromes: motor nerve conduction may be somewhat slow, or it may be normal. In any case the degree of slowing will be uniform throughout the length of the nerve in the arm. Except in mild cases the sensory action potential from the little finger will be reduced or absent.

(5) Cervical cord lesions and motor neurone disease: changes in motor nerve conduction velocity have generally been small, and slowing, when it has occurred, has been distributed uniformly down the nerve. Sensory action potentials are usually preserved.

(6) Cervical spondylosis is a complex problem in that the lesion may affect the cervical root or the spinal cord, or both. We have only examined a small number of these patients,

but so far it is our impression that they behave more like spinal cord than peripheral lesions.

(7) Chronic polyneuritis and peroneal muscular atrophy: these usually show gross slowing of motor conduction velocity with a small or absent sensory action potential.

REFERENCES

DAWSON, G. D. (1956) *J. Physiol.*, **131**, 436.
——, and SCOTT, J. W. (1949) *J. Neurol. Psychiat.*, **12**, 259.
GILLIATT, R. W. (1955) *J. Neurol. Psychiat.*, **18**, 145.
——, and SEARS, T. A. (1958) *J. Neurol. Psychiat.* In the press.
——, and WILSON, T. G. (1954) *J. Neurol. Psychiat.*, **17**, 104.
SIMPSON, J. A. (1956) *J. Neurol. Psychiat.*, **19**, 275.

[*November* 13, 1957]

## DISCUSSION: HYDROTHERAPY. IS IT OF VALUE?

**Dr. R. Harris** (Buxton):

During the period 1909–1931 a serious attempt was made to put hydrotherapy, and other forms of physical treatment, on a rational basis. It is clear that physical medicine owes a great deal to balneology (or hydrotherapy as we call it to-day). Fifty years ago the British Balneological and Climatological Society joined the Royal Society of Medicine to become its Section of Balneology and Climatology (1909). This Section in 1931 gave place to the Section of Physical Medicine.

In preparing this paper I attempted a critical survey of experimental work done on hydrotherapy and the quality and volume of physiological experiment I found fifty or more years ago surprised me. For instance, Kellog of Philadelphia (1904) set out to answer a number of questions—what do hot and cold baths and douches do to temperature control and working capacity? His apparatus, although cumbersome compared with electronic machines, was accurate enough to give reliable answers. He used full bath calorimeters, continuous rectal temperature measurements and simple mechanical ergometers to study his problems. A subject whose "working capacity" was initially 6,480 lb. was given a hot bath (112° F.) for 12 minutes with a 16% decrease in work output. Following a cold spray douche (50° F. for 30 sec.) his working capacity was restored to its initial capacity. In another subject work output was recorded continuously until fatigue was established and output fell. A cold douche (60° F.) was given and the ergogram showed a 44% increase. In other similar experiments a hot douche (112° F. for 15 sec.) decreased work output by 33%, neutral baths had no effect, and cold baths produced a 48% increase in performance. A further experiment, which further illustrates the restorative effects of cold douching, was that of a man whose initial working capacity was 6,870 lb. He rode 35 miles on a bicycle in two and a half hours. His working capacity was then measured and showed a 13% reduction in performance, which was restored to its initial value after a half-minute hot shower and a half-minute cold douche.

These experiments of half a century ago demonstrate clearly the potency of these agents. A massive volume of similar experimental work, mainly on the Continent, has been performed on the physiological effects of various applications of water—as baths, douches and sprays—hot, cold and neutral or alternating—and results expressed in terms of ergometry, plethysmography, electrocardiography and biochemistry, and by study of the blood pressure, pulse or respiration rate, urine volume and analysis, blood sugar and leucocyte count.

What I have failed to find is accurate assessment of the *clinical* value of these proceedings. This is perhaps not surprising. Hydrotherapeutic measures have, in general, been used in conditions with obscure pathology—labelled "chronic rheumatism," "sciatica", "fibrositis"—conditions well known to have variable courses, but being in the main self-limiting. In these the enthusiasm of the physician and the impressive ritual of hydrotherapy are valuable additions to the therapeutic effects of water. In the great days of the spas, hydrotherapy was itself considered to be a complete system of medicine and given for every illness. Often no treatment other than water internally and externally was given. Unfortunately neither the diagnostic criteria of that era, nor the methods of assessing

clinical results are acceptable to us. To-day hydrotherapy is no longer used alone but in conjunction with other forms of physical treatment and with drugs and general care. The tendency is still to use it in conditions of inexact diagnosis and pathology, and of relatively unknown natural history and prognosis—just the conditions in which quackery thrives, and in which accurate assessment of progress is so notoriously difficult. In these diseases and disorders even the clinical effect of drugs—a much simpler problem than that of physical therapy—is difficult to evaluate. Gold has been given for twenty-five years to patients with rheumatoid arthritis, and its value is still not known. Only this year has the Empire Rheumatism Council set up a properly controlled trial to provide an answer.

There is particular difficulty in assessing the *additional* value of a treatment when other treatments are being given at the same time. Recently we attempted to assess the value of wax baths in the treatment of the hands of in-patients with rheumatoid arthritis (Harris and Millard, 1955). Despite a complicated and detailed comparative study of 100 subjects followed for six weeks our results showed little difference between the treated and locally untreated groups. The basic regime which all the patients were having was responsible for all the gain in the locally untreated group, and most of it in the locally treated group. This is a simple example of the enormous difficulties we face in assessing the value of physical agents.

The internal use of water, by either drinking prescribed amounts of spa water, or introducing it into the body cavities has largely been abandoned and need not be discussed. "Ritual immersion" in waters considered to have specific therapeutic properties by virtue of their mineral content or radioactivity is no longer taken seriously in this country. The two principal aspects of its current use are as an exercise medium, and as a means of applying thermal or mechanical stimulation.

As an exercise medium I would agree with Coulter and Piersol (1950) that "in every condition in which the force of gravity is too great a handicap for weakened muscles the therapeutic pool is indispensable". Any hospital handling locomotor disabilities, be they rheumatic, traumatic or neurogenic, and Units where reconstructive and orthopædic surgery is practised, need pool facilities for exercise.

I am convinced of the great value of water as an exercise medium, for providing assisted, weight-eliminated or resisted exercise for paresed muscles as in poliomyelitis, and for exercising limbs where both joint and muscle are involved, as in rheumatoid arthritis. All of us have seen limbs which were clinically paralysed move in water, and I am sure that most of us have seen joints which were clinically fixed move in warm water. Relaxation of muscle spasm in neuromuscular disorders such as cerebral palsy and disseminated sclerosis can be demonstrated to anyone's satisfaction if they put such a patient in an ordinary hot bath. I know of no work which *proves* the value of pool techniques. It is not sufficient to say that the proof is clinically obvious. At one time few denied the virtues of blood letting for almost any disease: the clinical opinion then was that it was invaluable. Will a patient with poliomyelitis gain his maximal muscle power and function more quickly by exercise in water than by "dry" resisted exercise? Will the end point be the same? The patients themselves feel that exercise in water is more beneficial to them, and they would rather miss any other form of treatment than pool therapy. Patients with rheumatoid arthritis can start walking in the pool when they are not capable of weight-bearing, or even standing alone on dry land. Clinical impression and common sense indicate that this is valuable and probably leads to earlier "real" walking—but is this actually so?

Relaxation of spastic muscle takes place in warm water. Is it maintained for any useful period after leaving the pool, or can it be more efficiently produced by simpler techniques such as dry heat, or moist packs? We have recently tried to measure the relaxation produced by warm pool therapy in patients with ankylosing spondylitis. The patient's spinal profile was plotted with a posture-meter (Harris, 1955) before and immediately after thirty minutes relaxation and exercise in the deep pool, and after a further thirty minutes hot packing. The serial profiles showed real improvement in posture at each stage, and a gain of over 1 in. in height. However, we have repeated these measurements on the same subjects before and after relaxation exercises in the gymnasium—with almost exactly similar results.

Another group of patients for whom we have been using the pool are those with peripheral vascular diseases. In the limb with inadequate venous return, where stagnation and ulceration can only be controlled by bandaging or elastic stockings the external pressure of water supplies the necessary support, and exercise can be given to the foot and ankle in the weight-bearing position without the restriction of bandages, and the ankle mobilized. I am convinced that this is valuable, but my impressions are not proof.

The use of pools has received almost universal favour, and is now hardly considered "hydrotherapy". When hydrotherapy is criticized what is usually meant is the use of

water to supply skin stimulation by sprays, douches, contrast baths and whirlpool and aerated baths. There has been sufficient experimental work to demonstrate the physiological effects of hot and cold water on the body. The short-acting cold douche produces an initial peripheral vaso-constriction which is followed by hyperæmia and a feeling of well-being. There is, however, no clinical evidence to support its use in prophylaxis or in therapy.

Contrast baths, in which limbs are alternately immersed in hot and cold water have traditionally been used in conditions in which vascular spasm is present. There is no evidence that the passive exercise of dilating and constricting skin vessels has any value, and indeed it is probable that the benefit, if any, is due to the warm phase alone and that the cold phase may be dangerous. This has been recognized by gradual alterations in the technique of administering contrast baths: to-day the cold phase has gradually been shortened and the warm stage increased.

Fricke and Gersten (1952) studied the effects of contrast baths on the vasomotor response of rheumatoid arthritics. Although after a course of treatment the cold sensitivity of the rheumatoids was reduced there was little evidence of "re-education of the skin vessels", there was no correlation between this and clinical improvement and none of their patients showed marked clinical relief.

A critical study of blood flow measurements comparing effects of hot whirlpool and non-agitated baths at the same temperature has shown no difference between the two (Cohen *et al.*, 1949). However, it is again common experience that these baths feel more comforting to the patient and can be tolerated at higher temperatures.

Is the mechanical stimulation of falling water, of air bubbles, of rapidly altering thermal stimuli of value? Counter-irritation is a great standby of physical therapy, but again carefully controlled evaluation is lacking.

Let us not forget that some forms of hydrotherapy which were of value in their day have disappeared. In the era before phenobarbitone and the tranquillizers, the mental hospitals found the neutral bath a valuable sedative. The hydrotherapy department, like the padded cell and the strait jacket, has disappeared from the mental hospitals. One of the very few controlled clinical experiments I have found is on the effect of cold baths on typhoid fever. In New York Hospitals the mortality in a series of 900 cases was reduced from 16% to 7·75% by their use (Baruch, 1920). With effective drugs available this treatment is no longer necessary.

What are we left with in hydrotherapy? There is nothing in use of which the clinical value has been demonstrated by trials which will stand up to critical assessment. We have only overall clinical impressions—that exercise and relaxation in warm water is useful in the locomotor diseases and disabilities, and that the more exotic forms of hydrotherapy combined with spa ritual are useful in psychosomatic disorders.

May I, in this Jubilee Year of the Royal Society of Medicine, refer to the proceedings of the British Balneological and Climatological Society of 50 years ago? Dr. Solly of Harrogate, in a long debate on whether or not gouty patients should be treated in "salty" spas (Solly, 1907). . . . "wished to recognize fully the value of scientific experiment and felt it was obvious that no improvement in knowledge could be obtained without it . . . but many things to which scientific research seemed hostile after all turned out to be practically useful. . . . He fell back on the experience not of medical men, but of the patients." In a further paper on "The Influence of Climate upon Gout, Rheumatism and Rheumatoid Arthritis", Buckley (1907), of Buxton, suggested that owing to the lack of information on this the large centres should jointly publish their statistics.

Controlled clinical trials are urgently required in hydrotherapy. These must be done on a multi-centre basis so that adequate numbers of cases can be studied in a reasonable time and single and relatively simple problems dealt with one at a time.

## REFERENCES


BARUCH, S. (1920) Hydrotherapy. Philadelphia and London.

BUCKLEY, C. W. (1907) *J. Balneol. Clim.*, **11**, 67.

COHEN, J., MARTIN, G. M., and WAKIM, K. G. (1949) *Arch. phys. Med.*, **30**, 212.

COULTER, J. C., and PIERSOL, G. (1950) In: Handbook of Physical Medicine and Rehabilitation, A.M.A. Philadelphia and Toronto; p. 192.

FRICKE, F. J., and GERSTEN, J. W. (1952) *Arch. phys. Med.*, **33**, 210.

HARRIS, R. (1955) *Ann. Rheum. Dis.*, **14**, 90.

——, and MILLARD, J. B. (1955) *Ann. Rheum. Dis.*, **14**, 278.

KELLOG, J. H. (1904) Rational Hydrotherapy. Philadelphia.

SOLLY, E. (1907) *J. Balneol. Clim.*, **11**, 30.

**Dr. J. H. Jacobs** (London):

In the minds of most doctors, hydrotherapy has been almost entirely associated with spa treatment, yet most spa practitioners in this country have only made moderate claims for this mode of treatment. Yeoman (1951*a*) stated: "Many attempts have been made to justify specific claims for particular waters by scientific methods, but few will stand up to critical investigations. Certainly, various natural waters taken internally have an action on the body depending on their mineral contents, but so has a solution of these minerals made up by a pharmacist." He went on: "All will agree that, used externally, they produce their effect entirely owing to their mechanical and thermal properties." This rational statement is somewhat at variance with the literature still put out by the spas themselves. I quote from a brochure from one of our most famous spas. It is headed "Sulphur Baths", and reads—"These are the baths upon which, together with the waters, the reputation of . . . has been built. There are two distinct varieties, saline sulphur and alkaline sulphur water, which are used in different types of disease. The former is used chiefly in gout, rheumatism and liver disorders, and the latter in diseases of the skin."

The insistence on the word "cure", so dear to Continental Spas and so unwise when applied to the treatment of the rheumatic diseases, may be one of the reasons why Dr. Yeoman (1951*b*) writes in another article: "The decision to send a particular patient to a spa depends on the advice of the general practitioner or consultant, but it is remarkable how frequently it is the patient who initiates the idea." Perhaps this state of affairs results from the layman being rather more susceptible to pseudo-scientific propaganda than the more sceptical professional mind.

My own experience of hydrotherapy is largely limited to the treatment of the rheumatic disorders at the Arthur Stanley Institute, London, and, more recently in an investigation into the importance of hydrotherapy in a general department.

Firstly, our own minds and the mind of the patient must be quite clear on what is to be gained from this method of treatment. The patient must realize that no magical properties exist in water, and that any improvement in his condition can only be brought about by his active co-operation, and by using such muscle power as he possesses to its best possible advantage. From the physician's point of view, an accurate diagnosis is essential, and the treatment of such vague conditions as fibrositis, neuritis and panniculitis can only bring hydrotherapy into disrepute. The beneficial results he hopes to gain will be achieved solely through the hydrodynamic and thermal qualities of water. One cannot entirely leave out the psychological value of pool therapy—to the patient who may be dispirited by his previous efforts it is something new and novel, and its ritual impressive. The fact that the patient is able to use weakened muscles which otherwise may still seem to him to be paralysed, and also that early ambulation is possible, enhances the patient's confidence, increases his morale and stimulates him to further efforts.

Exercises can be graded from water-assisted to water-resisted, depending on the methods employed. In addition, the buoyancy of the water enables a range of assisted movements to be obtained in any direction, which is especially helpful in early joint mobilization. This mechanical property of water also enables heavy patients to be handled with greater ease once they are in the pool, and makes possible limited weight-bearing ambulation in the early stages of rehabilitation. Increased weight-bearing may conversely be brought about by gradually decreasing the depth of the water in the walking lane.

Of all the possible benefits to be derived from hydrotherapy, early ambulation with limited weight-bearing and the consequent early re-establishment of co-ordinated patterns of movements seems to me to be the most important—this one facet of hydrotherapy is difficult to duplicate by any other alternative method.

Hydrotherapy should be considered as a form of exercise therapy which is particularly suited to the treatment of weakened or partly paralysed muscles, but graduation to other and more vigorous forms of exercise which can be adapted to greater and maximal resistance should take place at the earliest opportunity. However, the re-education of individual muscles rather than of patterns of movements is probably more easily carried out on dry land than in the pool, owing to the difficulty of fixing and stabilizing joints in water.

The beneficial effect of heat in relaxing muscle spasm prior to exercise therapy is well accepted. The warm pool at 94° to 98° F. enables one to carry out re-educational procedures on relaxed muscles, and to obtain a maximal range of joint movement without, as Lowman (1957) puts it, the occurrence of "the pain-spasm-pain cycle". A temporary increase in peripheral blood supply occurs during the short period of immersion, but whether this is of any lasting value is a matter for speculation.

In considering the place of pool treatment in a general department the treatment of paralytic poliomyelitis immediately springs to mind, but these cases rarely appear in a general hospital within the first few months of their onset, when hydrotherapy would be

most beneficial. In the later stages other forms of exercise therapy are probably of equal or more value.

There is, of course, no place for hydrotherapy in the management of the acute stage of rheumatoid arthritis; it is the chronic patient with polyarticular involvement, stiffness, and a limited range of joint movement who is most likely to be helped in the pool by means of walking exercises, muscle re-education and by increasing the range of movements of his stiffened joints. Fortunately, with the provision of modern drugs and the availability of intra-articular hydrocortisone, these more crippled cases of rheumatoid arthritis seem to be less prevalent in general hospitals than in former days.

In osteoarthritis, it is the patient with hip involvement who is most likely to benefit from hydrotherapy. Much of the pain in the hip is secondary to capsular fibrosis and contraction, and in the warm medium of the pool it is possible to obtain adequate relaxation, which enables the physiotherapist to put the joint through an increased range of movement, and so stretch the capsule and at the same time exercise and strengthen the prime movers of the joint. I doubt whether the results so obtained are superior to those obtained with short-wave therapy and sling exercises. In post-operative orthopædic conditions, especially those involving the hip-joint or fractures of the lower limbs, hydrotherapy has its part to play by ensuring early walking re-education, preventing and reversing muscle atrophy, and avoiding osteoporosis due to prolonged disuse.

Of the spastic neurological conditions, hemiplegics benefit from early ambulation and relaxation provided they are fit enough to undergo pool therapy, and cases of multiple sclerosis, in whom weakness is the predominant feature, may also benefit, provided their balance is reasonable and their sphincters controlled. Hydrotherapy in cases of cerebral palsy is of doubtful value. To judge the size of this problem in a general hospital, I have been looking through the records of the new patients who have been attending my department for the past few months, and only 5% fall into the categories I have mentioned. In addition there are always a number of more chronic patients who would also be suitable for hydrotherapy.

Therapy in a well-equipped pool is expensive in money, time, space and in personnel, though admittedly a certain amount can be done in smaller tanks. Pool therapy can be most exhausting for both the patient and the hydrotherapist, and this factor also must be considered.

One must inevitably face the question as to what can be achieved with hydrotherapy that cannot be achieved in a department which is not equipped with a pool, for this is the case in most units of Physical Medicine in general hospitals. I have already stressed the benefits of early ambulation with limited weight-bearing, and perhaps one should also stress the treatment of the patient suffering from chronic poly-articular rheumatoid arthritis, but apart from these two categories, I doubt if hydrotherapy is superior to other and more readily available alternative methods of treatment.

I feel it is fair to say that in a general hospital a pool is a desirable facility, though by no means an essential one. Finally I should like to add that unless all concerned with this method of treatment, including the patient, have a clear picture in mind of the aims of hydrotherapy, its abuses may well outweigh its uses.

## REFERENCES

LOWMAN, C. L. (1957) *Physioth. Rev.*, **37**, 224.
YEOMAN, W. (1951*a*) *Proc. R. Soc. Med.*, **44**, 283.
—— (1951*b*) *Med. ill.*, **5**, 328.

**Dr. T. G. Reah** (Harrogate):

In June 1957 we held a meeting of the Section of Physical Medicine to discuss breathing exercises. In the discussion a clinician was firmly convinced and two other speakers were doubtful of their value. It was generally agreed that there was little or no change in the objective movements of the chest after a course of exercises, and although many patients are encouraged by them, we ultimately remained ignorant as to whether or not they were useful. In respiratory disorders it is difficult or impossible to obtain comparable series of patients for trials by different methods of treatment and in any case a double-blind trial of exercises is impossible.

In general medicine there are innumerable instances of the value of a particular treatment so that regardless of control series, double-blind trials and the statisticians we accept for instance the value of digitalis and mercurial diuretics in congestive heart failure. Also, the value of the newer preparations of insulin has been largely established by observations on

individual patients and groups of patients. So it has been and still is with many of the individual forms of treatment given in Departments of Physical Medicine and we know how many electrotherapeutic measures have been abandoned as valueless and others retained while in hydrotherapy we have discarded aerated, foam and whirlpool baths.

A consideration of physiological, anatomical and mechanical principles will often suggest whether a form of treatment will help and thereafter continued observations of the patients will frequently decide for us if such a treatment is producing a quicker and better result than either no treatment at all or than some other measures would have produced. Empiricism or the practice of medicine founded on experience particularly when tempered by a critical outlook and an acute awareness of our basic obligations to patients is still worthy of a place in medicine.

It is with such an outlook that I approach the question of the value of hydrotherapy in the treatment for disorders of the locomotor system. Many patients who come to us are sent from other hospitals both teaching and non-teaching, and with few exceptions are suffering from rheumatoid- or osteo-arthritis. There is often the comment that they have had prolonged treatment at home and they are now being sent to us for the benefit of the other forms of treatment, mainly hydrotherapy, that we are able to give. After their first visit such patients are frequently sent again to us because of the improvement in their mobility that has been achieved. I realize that in addition to the various forms of therapy there is the advantage of the rest in hospital and the change in the patient's general environment.

If we accept the use of heat as a therapeutic measure—and which of us has not in our younger days, after strenuous exercise, relaxed stiff and aching limbs in a hot bath—we have to acknowledge that such measures as immersion baths, particularly when combined with under-water douches at a higher temperature than that of the bath, and the use of media such as mud and peat, are of value. It might be possible to treat a group of patients suffering from osteoarthritis of the knees or hips and compare and contrast the results with those obtained in other groups treated by simple analgesics or by electrotherapy. The results could be difficult to assess if it were found that in one group of patients there had been a greater average loss of weight than in the others, because whatever else may be done weight reduction is essential in these usually overweight patients. With rheumatoid arthritis it would be, in my opinion, much more difficult to assess the results because of the natural or drug-induced variations in the activity of the disorder. Dr. Harris has told us of how in 1955 with Dr. Millard he made a comparative study of the treatment of the hands in rheumatoid arthritis. In three groups of subjects one group had no local treatment, and in the other two groups paraffin wax baths and packs were given. We know that they concluded paraffin wax baths are of little value in the treatment of rheumatoid arthritis. In this investigation they used the dipping and packing method instead of the original continuous immersion bath. Several years ago we used the dipping and packing method but quickly discarded it because our own observations suggested, and the experienced patients insisted, that it was not as effective as the original method. I should be grateful to know if Dr. Harris has pursued the investigation of the original technique as suggested in the paper as it would confirm or refute our clinical impressions.

When we were able to install a Hubbard Tank and certainly without being able to control our observations we were quickly of the opinion that those patients treated in it progressed more rapidly than those treated by other methods. There was no reason why we, the physiotherapists, or the patients should have been susceptible to suggestion because for the physiotherapists it meant more work and many of the patients had first to be persuaded to try it. The results were so clinically impressive and so increasing were the demands upon the tank that we asked for a deep pool. After four years' experience with the deep pool we have now asked for another.

Deep pools are expensive to construct and it has been difficult to obtain accurate estimates of the cost of our pool because it was built within the structure of an existing building and the main services were already easily available. Its construction and the provision of the filter plant and ventilation plant installations cost about £6,000. The estimated cost of a new department for physiotherapy and hydrotherapy which we are considering is £30,000 of which about half is for the proposed new deep pool with its heating and filtration plant and the necessary adjacent accommodation. We feel that the patients will derive as much value from one side of the building as from the other.

Last year the cost of maintenance of a deep pool was £700 but an adjustment of the heating apparatus has been made which it is estimated will reduce the annual cost to around £500.

In the pool patients are stripped so that all movements are continually under the observation of the physiotherapists and trick movements, for which most patients seem to

have an almost infinite inherent capacity, while more easily performed in the pool than on slings are more readily detected and corrected.

The relief from pain and diminution of muscle spasm on immersion in warm water are also important in that the range of painless movements is increased and this is not reproducible in any form of dry treatment. The adjustment and manipulation of the patients, particularly those who are most incapacitated and those who are obese, is much easier in water and much less arduous for those treating the patients. If we are to compare the value of a form of hydrotherapy with any other form of treatment we must take account of the amount of skilled supervision required and we have found that two physiotherapists working in a pool can treat in the same time about the same number of patients as they supervise in other forms of treatment. Incidentally, we have also found that a partnership of two physiotherapists working together in the pool is much more efficient and satisfactory than one working alone.

While individual muscles or groups of muscles may be re-educated by other means, co-ordinated movements to produce a natural movement such as arising from a chair are much more satisfactorily taught in water than on dry land. Such training may, in our experience, be relatively easily taught in water, difficult to teach on dry land and impossible to teach in the slings. Walking exercises without the use, or rather, the encumbrance, of crutches, are possible in water; and in the treatment of some patients suffering from the effects of poliomyelitis, we have found that walking exercises in water may be performed with the help of spinal and other supports which would otherwise have been impossible. Also, once accustomed to the pool, patients appreciate its value and although we have patients returning regularly and asking for further courses of treatment in the deep pool, we have not yet had one coming back and asking again to go on the slings.

For example one patient, a woman of 42, was first seen by me eight months ago. When 2 years old she had poliomyelitis affecting the lower limbs and she is later said to have walked with calipers, but at the age of 14 years she deteriorated and from her 18th year she had been almost completely helpless. She was in a spinal chair unable to move her head or to sit up, with a complete flaccid paralysis of the lower limbs, and only limited movements of both upper limbs were possible. Both the patient and the physiotherapist were enthusiastic to see what could be done in the deep pool, spurred on, I think, by my deliberately unconcealed scepticism. After a few preliminary immersions she was fitted with a polythene jacket and a head piece and began with much assistance to walk in the water. Then in water to axillary level she dispensed with the head-piece and recently she has been for a car ride sitting up with the head supported only by a pillow and able for the first time for over twenty years to look around her.

Another patient, a woman aged 49, was found eight years ago to have bilateral protrusio acetabuli with osteoarthritis of the hips and in the following five years her pain and incapacity increased although she was having regular treatment. Three years ago she began to have treatment in the deep pool and since, with four weeks' treatment each year, she has not further deteriorated.

**Dr. Harris,** in reply to Dr. Reah's question about paraffin wax baths, said that he and Dr. Millard studied only wax packs, and not baths. Continuous immersion in wax was the technique used when wax was first introduced, but for convenience most hospitals had replaced this by dipping and packing. This was the particular technique they had investigated; but continuous baths might be more effective. They themselves used continuous immersion baths as a routine for feet, but in practice continuous wax baths for the hands were uncomfortable as they usually necessitated patients sitting in awkward positions for thirty minutes.

# Section of Experimental Medicine and Therapeutics

President—J. V. DACIE, M.D., F.R.C.P.

[*October* 8, 1957]

## Methods of Measuring Pulmonary Diffusing Capacity and their Significance

By ROBERT MARSHALL, M.D., M.R.C.P.

*Oxford*

THE function of the lungs depends partly on their bellows action producing an adequate ventilation of the alveoli and partly on the ability of the lungs to transfer oxygen from the alveoli into the blood and $CO_2$ from the blood into the alveoli. This transfer occurs solely by diffusion and the gas with whose diffusion we are most concerned is $O_2$. The diffusing capacity of the normal resting lung is sufficient to supply about three times the normal resting $O_2$ uptake but this capacity has to increase in order to deal with the $O_2$ uptake required by even moderate exercise. Thus the reserve of the diffusing capacity for $O_2$ is small and if the diffusing capacity is impaired by disease respiratory failure may occur. $CO_2$ on the other hand diffuses over twenty times more rapidly than $O_2$ so that the elimination of $CO_2$ is never limited by diffusion, and $CO_2$ retention, when it occurs, is due to inefficient ventilation, not to impaired diffusion.

The diffusing capacity of the lungs for a gas is defined as the millilitres of that gas which can be transferred from the alveoli into the blood, per minute per mm.Hg pressure difference between the alveoli and the blood. The resistance to this diffusion is provided by the alveolar membrane which is normally less than $2{\cdot}5\mu$ thick and consists of the alveolar epithelium, a complex basement membrane and the capillary epithelium. The ease with which gas passes through this membrane, that is, its diffusing capacity, depends on the thickness of the membrane and the actual surface area separating the air and the blood. Any increase in thickness of the membrane or reduction in size such as would be produced by a reduction in the number of functioning alveoli or capillaries, will reduce the diffusing capacity.

The ideal measurement of diffusion to make is the diffusing capacity for $O_2$ but this method presents a number of technical difficulties. CO behaves similarly to $O_2$ in its uptake by the blood and many measurements of diffusing capacity are now made using small concentrations of CO which can be measured very conveniently with an infra-red gas analyser.

There are several differences in the behaviour of $O_2$ and CO which are of importance. First, CO is less soluble than $O_2$ in body fluids and the molecule is slightly smaller; the net result is that $O_2$ diffuses 1·23 times more rapidly through membranes than does CO (Fig. 1).

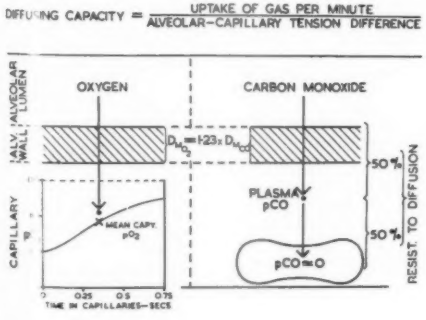



FIG. 1.—Measurement of the diffusing capacity for oxygen (left) and for CO (right). $D_{M_{O_2}}$ and $D_{M_{CO}}$ are membrane diffusing capacities for oxygen and CO respectively. $pO_2$ and pCO are the tensions of oxygen and CO respectively.

Secondly, the rate of combination of $O_2$ and hæmoglobin is three times faster than that o CO and hæmoglobin, but carboxyhæmoglobin breaks down very much more slowly han oxyhæmoglobin so that the carboxyhæmoglobin, once formed, exerts a negligible ack pressure of CO in the plasma. In calculating the diffusing capacity for CO, the capi lary tension is taken as zero and the uptake divided by the alveolar tension gives the diffu sing capacity. It is this ability to neglect the pressure of CO in the red cells that makes the c lcu-lation of the diffusing capacity for CO so easy and which has led to its widespread use. Forster, Roughton and others have been able to show that in normal subjects only a bout 50% of the resistance to the transfer of CO is due to diffusion through the membrane and the other 50% is produced by the slow rate of combination of CO with hæmoglobin. Thus the diffusing capacity normally measured with CO is not only a measure of diffusion thr ugh the membrane; it includes this extra resistance. The diffusing capacity for oxygen al o is not simply the diffusing capacity across the membrane. The proportions of the total resistance to diffusion offered by the membrane and by the red cells cannot be measured as in the case of CO but $O_2$ passes through the membrane 1·23 times more easily than CO and is taken up by the red cells three times more rapidly. Thus, if the resistance of the membrane is 50% and the resistance of uptake into the red cells is 50% of the total resistance to CO diffusion, then the corresponding proportions for $O_2$ would be 70% in the membrane and 30% in the uptake by the red cells.

## Methods of Measuring the Diffusing Capacity

(1) *The diffusing capacity for oxygen* ($DO_2$).—The factors to be measured are illustrated in Fig. 1. Although the alveolar gas is not usually uniform the mean alveolar oxygen tension can be calculated indirectly. The mean pulmonary capillary $O_2$ tension has to be calculated by Bohr's integration procedure from the mean alveolar $O_2$ tension, the $O_2$ tension at the beginning of the capillary, the tension at the end of the capillary and the oxyhæmoglobin dissociation curve. The tension at the beginning of the capillary can be estimated but the tension at the end cannot be measured because, before the blood can be sampled in the artery, venous blood may be mixed with it and this will produce a considerable fall of tension when the subject is breathing air. By breathing a low $O_2$ mixture this effect of venous admixture can be minimized and also the tension gradient between the alveoli and the end of the capillary is increased and the error of measurement is reduced. Thus measurement of $DO_2$ requires arterial blood and gas samples to be collected when the patient is breathing air and when breathing a low $O_2$ mixture. The tension of $O_2$ and $CO_2$ in the arterial blood have to be measured by the microtonometer technique developed by Riley—a technique which requires considerable practice and dexterity.

If the measurements are made on exercise it is found that the $DO_2$ reaches a maximal value at an $O_2$ uptake of about 1 litre per minute and this maximal $DO_2$ is considered to be of more value clinically than the resting $DO_2$ since at rest only a part of the lung's diffusing capacity for $O_2$ is being measured. The disadvantages of this method of measuring the diffusing capacity are that it takes a considerable time, the techniques are not easy and the need for an arterial puncture makes the method unsuitable for repeated use on patients. It is for these reasons that measurement of the diffusing capacity for CO has become popular.

(2) *The diffusing capacity for carbon monoxide* (Dco).—Two types of method are used, the single breath method and the steady state methods.

(*a*) *The single breath method:* This was first used by Krogh in 1915 and the technique has recently been improved by Ogilvie and others (1957). The subject breathes out as far as possible and then takes a deep breath of a mixture containing about 0·15% CO, 10% helium and 20% $O_2$; the remainder being nitrogen. The subject holds the breath for 10 seconds and then expires rapidly. The first few hundred millilitres of expired air are discarded and the remainder collected and analysed for CO and helium. The helium, which is not absorbed in the lungs, acts as a marker gas and makes it possible to calculate the initial concentration of CO in the lungs. The Dco during breath holding can be calculated from the alveolar volume and from the initial and final concentrations of CO in the lungs. This method is very simple and quick to carry out, it gives repeatable values and it does not require arterial puncture. Measurements on patients can be made only at rest.

(*b*) *Steady state methods:* The uptake of CO over a given time is measured as the difference in the amount of CO inspired and that expired: the uptake per minute, divided by the mean alveolar tension of CO, gives the Dco. Two methods have been devised and they differ in the ways by which the mean alveolar tension of CO is obtained. One method, described by Bates *et al.* (1955), uses the concentration of CO in the end tidal sample as a measure of the mean alveolar CO. This method is valid in normal subjects but it is not valid in patients, such as emphysema patients, who have unequal mixing of gas in the lungs. Experiments were carried out in which subjects breathed air containing a small amount of CO for several

minutes until they were in a steady state. End tidal samples were taken during several breaths and then, at the end of a normal inspiration, the subject expired fully into a tube of 1 in. bore and 16 ft. long in which the air was trapped and samples taken at intervals.

In normal subjects the concentration of CO in the samples at different parts of the tube, when corrected for the time of expiration, was uniform and was the same as that of the end tidal sample. In patients with emphysema, on the other hand, the farther the subject expired the lower the concentration of CO. The end tidal sample is higher than the mean alveolar CO and if it is used for calculation of the Dco, it will give falsely low values.

The other steady state method is that described by Filley *et al.* (1954). The mean alveolar tension of CO is calculated by assuming that the dead space for CO is the same as that for $CO_2$ and the $CO_2$ dead space can be calculated if the $CO_2$ tension in the expired air and the arterial $CO_2$ tension are known. This method, as originally described, requires an arterial puncture. In a modified method the arterial $CO_2$ tension is calculated from the mixed venous $CO_2$ tension, this being obtained by rebreathing a gas mixture containing approximately the same tension of $CO_2$ as that expected in the venous blood. This modification avoids the arterial puncture but it can be used only for measurements at rest.

## Comparison of Methods of Measuring the Dco

In normal subjects different ranges of values have been reported when using different methods of measuring the Dco and in patients with emphysema the steady state method using end tidal samples gives uniformly low results. With the single breath method about half the emphysema patients studied have a normal Dco. Some experiments were carried out to investigate these differences. The single breath method is usually carried out at full inspiration and this gives higher values than if the measurements are made at smaller lung volumes. In a series of normal subjects the steady state method gave values similar to those of the single breath method when the breath was held at about the functional residual capacity.

A series of patients with emphysema were investigated by the single breath method; some patients had normal and some had low Dco values. By the steady state method using end tidal samples all these patients had a low Dco. The results obtained by the modified Filley's method agreed fairly well with the single breath method when allowance was made for the smaller lung volume at which the measurements were made. The single breath and Filley's methods correct for uneven distribution of gas in the lung and the diffusing capacities of different parts of the lung affect the result equally, irrespective of whether they are under- or over-ventilated during normal breathing. If a part of the lung is poorly ventilated it will be able to take little part in gas exchange even though its diffusing capacity, as measured by these methods, is normal. The diffusing capacity of the lung measured using end tidal samples is not a measure of diffusion alone; it is affected both by diffusion through the membranes and also by unequal ventilation of the lung which gives a falsely high figure for the mean alveolar CO. For this reason low values are obtained in diseases in which the diffusion may or may not be reduced but in which the ventilation is very uneven, as in emphysema, and the results have been found to be of value in assessment of the prognosis of such patients (Bates *et al.*, 1956). But the measurement is not a measurement of diffusion alone and in such patients should not be expressed in the units ml. CO per minute per mm.Hg.

## Comparison of the Dco and $DO_2$ Results

We may decide, for technical reasons, to measure the Dco but we really want to know the diffusing capacity for $O_2$ and it is of interest to see how these two measurements compare. The Dco is a measure of the diffusion from the alveoli to the red cells and only half of this resistance to diffusion is in the membrane and the other half is due to the slow uptake by the red cells. In Table I the predicted values for $DO_2$ are compared with the measurements

Table I.—Comparison of the Diffusing Capacity for Oxygen and For CO

*Subject: R.M.* Diffusing capacity ml./min./mm.Hg

| | Single breath Dco | | | Predicted $DO_2$ | Approx. membrane $DO_2$ |
|---|---|---|---|---|---|
| | Total Dco | Membrane Dco ($DM_{CO}$) | $DM_{CO} \times 1{\cdot}23$ ($\equiv DM_{O_2}$) | | ($DM_{O_2}$) |
| Rest (at F.R.C.) .. | 28 | 48 | 59 | 20 | 26 |
| Rest (full insp.) .. | 32 | 51 | 63 | — | — |
| Exercise (full insp.) ($O_2$ uptake 2·6 l./min.) | 46 | 70 | 86 | 60 | 73 |

$DM_{CO}$ = membrane component of the Dco.

$DM_{O_2}$ = membrane component of the $DO_2$.

of total Dco by the single breath method and the membrane component using the single breath method at different $O_2$ tensions (Forster *et al.*, 1955). The membrane component of the Dco multiplied by 1·23 should give the same value as the membrane component of $DO_2$. I have not measured $DO_2$ so I have had to compare the Dco with the predicted values of $DO_2$ but a rough comparison can be made. The Dco and the membrane diffusing capacity for CO were measured at rest and the membrane Dco multiplied by 1·23 gives a calculated membrane diffusing capacity for $O_2$ ($D_{M_{O_2}}$) of 59 which is over twice the $D_{M_{O_2}}$ calculated from the predicted $DO_2$. On exercise sufficient to increase the $O_2$ uptake to 2·6 litres per minute the membrane Dco rises to 70 which gives a calculated $D_{M_{O_2}}$ of 86; this is in comparison with a predicted maximal $DO_2$ of 60 and a $D_{M_{O_2}}$ of 73 for a person of this size. At present we do not know the reason for these different results. One possible explanation is that the $DO_2$ measures the diffusion only into those capillaries through which blood is flowing at the time that the measurements are made; the Dco will measure diffusion into any capillaries containing blood irrespective of whether the blood in them is flowing or stagnant. If only about half of the capillaries have a normal blood flow through them at rest this could explain the different results obtained by the two methods; on exercise the blood flows through more capillaries and the two values approach each other.

To conclude, although the Dco does not give a direct measure of $DO_2$ the technical advantages of measuring the Dco usually outweigh the disadvantages, particularly since, in practice, the two methods usually run in parallel and for clinical purposes reduction in diffusing capacity can be shown quite adequately by measurement of the Dco.

The single breath method of measurement of the Dco gives the same results as the other CO methods and as it is the easiest method to carry out it is the method of choice for measurements made at rest. Measurements made on exercise minimize the technical errors of the steady state methods but except for this reason I know of no advantage to be gained from measurement of the Dco on exercise. The result depends on the rate of exercise and the maximum value for Dco is reached only at fairly severe rates of exercise in normal people.

## REFERENCES


Bates, D. V., Boucot, N. G., and Dormer, A. E. (1955) *J. Physiol.*, **129,** 237.

——, Knott, J. M. S., and Christie, R. V. (1956) *Quart. J. Med.*, **25,** 137.

Filley, G. F., MacIntosh, D. J., and Wright, G. W. (1954) *J. clin. Invest.*, **33,** 530.

Forster, R. E., Roughton, F. J. W., Cander, L., Briscoe, W. A., and Kreuzer, F. (1955) *Amer. J. Physiol.*, **183,** 615.

Krogh, M. (1915) *J. Physiol.*, **49,** 271.

Ogilvie, C. M., Forster, R. E., Blakemore, W. S., and Morton, J. W. (1957) *J. clin. Invest.*, 36, 1.


# Oligopnœa [*Abridged*]


By P. Hugh-Jones, M.A., M.D., M.R.C.P.

*London*


The term "oligopnœa" was purposely chosen to mean an inadequate output of air from the lungs, just as "oliguria" is used for an inadequate or scanty output of urine.

*Some factors controlling ventilation.*—Before giving clinical examples of oligopnœa, their diagnosis and treatment, it is helpful to consider the factors controlling the normal "air output", or ventilation of the lungs. It is generally taught that this is chiefly regulated by the tension of carbon dioxide in the arterial blood. A rise of carbon dioxide tension stimulates the respiratory centre and leads to an increase in ventilation, while a fall in either oxygen tension or pH has a similar, though much less marked, effect. All this is undoubtedly true, but it is becoming apparent that nervous impulses from stretch receptors in the lungs play an equally, if not more, important role. Just as proprioceptive impulses from joints determine posture, reflexly in relation to muscle stretch, so these pulmonary stretch receptors regulate ventilation according to the degree of movement of the lungs. In disease, disturbance of reflexes from these receptors may become the primary mechanism which regulates ventilation, and this disturbance is readily accompanied by the sensation of "dyspnœa".

The significance of stretch receptors can most easily be demonstrated by a very ingenious experiment designed by Fowler (1954) which was concerned with the breaking point of breath-holding. It was held that the limit to voluntary apnœa was the rise of carbon dioxide and fall in oxygen tension in the blood causing extreme stimulation of the respiratory centre, and a number of papers had been published which defined these arterial blood gas-tensions when the limit to breath-holding was reached. Fowler got a spirometer and filled it with an "air" mixture containing oxygen and carbon dioxide at the same tensions as these gases would be in the blood at the limit to breath-holding. He asked a subject to hold his

breath for as long as possible and then to breathe in and out of the spirometer. Of course the subject's carbon dioxide tension then went on rising and oxygen tension falling but instead of feeling worse, he felt relief! After a while the subject felt uncomfortable breathing from the spirometer in this way, and was then asked to hold his breath again; soon he could hold it no longer and again he was told to breathe from the spirometer, and so on, until the total "breath holding" period was much prolonged. But from our point of view, the important thing is that every time chest movement was restarted relief was experienced, showing it was the lack of impulses from stretch receptors and not gas tensions which was of prime importance in the discomfort of breath-holding. And you can do this experiment now by simply stopping breathing; it becomes uncomfortable at once, long before there is a significant alteration in the gas tensions in the arterial blood.

It appears that if the stretch receptors either send no impulses or if they send excessive impulses the sensation is unpleasant. Excessive impulses occur when inspiration approaches the maximum possible depth (which again you can try now by taking in as deep a breath as possible). Excessive stretch of these receptors may be one of the many factors which appears to be responsible for the sensation of "dyspnœa" when ventilation reaches a certain proportion of the maximum possible ventilation, or maximum breathing capacity (Hugh-Jones, 1952).

Just as it has been shown by Fowler's experiment that breath holding is limited by stretch receptors rather than by blood gas tensions so there is increasing evidence that in some circumstances impulses from the stretch receptors, rather than blood gas tensions, regulate ventilation. These receptors send impulses from the lungs which are related to the work of breathing (Davies, Fowler and Lambert, 1956) and in disease states, for example emphysema, where the mechanics of breathing are disturbed and a given intrapleural pressure change may be responsible for a diminished air-flow in and out of the lungs, the patient may maintain a ventilation determined by keeping the work of breathing as low as possible, with his abnormal lungs, at the expense of maintaining normal gas tensions in his arterial blood. This is a common finding in emphysema where the patient readily complains of breathlessness if his ventilation is stimulated in any way (usually by exertion) and where the arterial oxygen is low and the carbon dioxide high when the patient is at rest. Yet such a patient, at rest, can often put his carbon dioxide tension back to normal by increasing his resting ventilation on command. Such patients Dornhorst (1955) has considered to be "lazy breathers". They are, in fact, in a state of chronic hypoventilation or mild chronic "oligopnœa".

*The effect of infection.*—The importance of mild chronic oligopnœa becomes much more apparent when the patient gets an acute respiratory infection. Any patient with a patchy bronchiolitis or bronchopneumonia has some parts of his lungs underventilated or even entirely unventilated, yet with blood still flowing in these areas. Thus, there is virtual "shunting" of venous blood into the arteries, in these underventilated areas. As a result of the increased carbon dioxide in the arterial blood, ventilation is augmented so that those parts of the lung in which air still flows are excessively ventilated. From them carbon dioxide can be eliminated, but the blood in them is already being fully oxygenated so their overventilation can only compensate for the rise of carbon dioxide in the arterial blood but not for the fall in oxygen caused by the presence of those areas of the lung with a normal blood flow, but reduced, or absent, air-flow. Hence the familiar picture of a cyanosed patient with pneumonia, breathing rapidly. If, however, the patient has altered mechanics of his chest as well as his pneumonia then, either because of excessive stimulation of the stretch receptors, or in some severe cases because of greatly reduced maximum breathing capacity, the ventilation is not adequately augmented and the patient becomes not only cyanosed but retains carbon dioxide. In other words, he develops acute oligopnœa, with relatively severe underventilation compared with his needs, even though he may appear to be breathing rapidly and hard. In such a patient, whose respiratory centre is no longer responding normally to carbon dioxide, the administration of oxygen for his cyanosis removes the remaining factor of anoxia, which was tending to maintain the little ventilation he had, so that his ventilation falls even further and leads to such high levels of carbon dioxide as to cause a comatose state to supervene on the disorientation from the previous lack of oxygen.

*Diagnosis.*—Clinically, the diagnosis of acute oligopnœa may not be easy; the mental state can be mistaken for that of a primary neurological condition such as a cerebrovascular accident, and the respiratory hypoventilation can be overlooked especially if there is rapid shallow breathing.

Just as the rise of blood urea is a useful confirmation of uræmia in states of oliguria, so arterial blood gas analysis confirms the carbon dioxide retention of oligopnœa. Another useful adjunct in diagnosis is to measure ventilation, just as one normally measures the urinary output for the diagnosis of oliguria; we use the very suitable anemometer designed

by Dr. B. M. Wright of the M.R.C. Pneumoconiosis Research Unit. It is small, virtually free from resistance, and can be used even with severely ill patients to chart their minute ventilation instead of simply charting respiratory frequency, which is, of course, not necessarily a reflection of the ventilation at all. With readings from this instrument, and the respiratory frequency, the alveolar ventilation can be calculated using an assumed value for the upper respiratory dead space. Then, the effects of oxygen and other therapeutic agents on the alveolar ventilation can be observed.

*Treatment of acute oligopnœa.*—Just as in oliguria arising from sulphonamides it is desirable to ensure a free passage for urine by flushing out the ureters by ureteric catheterization, so a free airway is the first essential in oligopnœa. In the patient with bronchopneumonia, secondary asthma is usually present, which is a major factor to air-flow obstruction. It is usually best detected by hearing the wheeze by auscultation over the throat, and treated by continuous aerosol inhalation of adrenaline or isoprenaline. This inhalation can be given at the same time as the oxygen which these patients badly need. We have seen patients in whom adequate aerosol treatment given with oxygen was itself enough to treat the hypoventilation. In all patients with central cyanosis from acute respiratory failure we give oxygen continuously and at a flow rate that is needed to remove cyanosis; if, on this regime, there is a tendency to acute oligopnœa, carbon dioxide retention, and drowsiness, then ventilation must be stimulated—either chemically, or if that fails, mechanically.

*Chemical stimulation of ventilation.*—Aminophylline (10 ml.) is given intravenously. It is a most useful drug in that it both acts as a central stimulant to ventilation and as an "antispasmodic" and we repeat it far more frequently than is customary, often two-hourly if that maintains adequate ventilation to prevent drowsiness from the oxygen and the patient gets no nausea with it. An alternative is intravenous nikethamide in similarly "heroic" doses of up to 5 ml. about two- or three-hourly depending on the clinical response. These injections, an aerosol of isoprenaline, and continuous oxygen successfully deal with the majority of patients who have acute oligopnœa on top of a chronic chest condition and literally save life while antibiotics have time to deal with the acute respiratory infection which usually precipitates this functional state. Nevertheless these patients are a serious medical emergency and if chemical stimulation is not completely successful and especially if abundant purulent sputum, or viscid secretion from status asthmaticus, prevents the maintenance of an adequate airway then we have no hesitation in performing a tracheotomy and using artificial mechanical ventilation.

*Mechanical ventilation.*—Tracheotomy is done under cyclopropane or intravenous barbiturate anæsthesia with Flaxedil as a muscle relaxant. With the tracheotomy tube in, adequate suction of bronchial secretions becomes much more practicable and a mechanical pump is used to provide the ventilation the patient needs.

A film, showing the first patient we artificially ventilated in this way, was projected at this stage:—

The patient was literally moribund, with cold extremities and feeble pulse, after a previous phase of high output heart failure of cor pulmonale. His respiratory rate of no less than 70 breaths per minute was associated with shallow abdominal breathing and negligible chest movement, and his severe oligopnœa was reflected by an arterial oxygen saturation 42%, carbon dioxide tension 74 mm.Hg, pH 7·32. Half an hour after tracheotomy blood analysis showed he had been over-ventilated by the pump because his carbon dioxide tension was then only 32 mm.Hg and his pH 7·63. Such over-ventilation can be dangerous and result in a further fall of blood pressure, especially if inadequate time is given in the respiratory cycle for venous filling of the heart. But after giving the correct ventilation his arterial blood was returned to normal (Fig. 1) and he was up and about in three weeks' time.

We find full humidification of gas going to the tracheotomy essential to prevent "crusting" in the trachea. If this is done there is little trouble with the procedure and simply by maintaining the arterial blood gases at normal through artificial ventilation, the heart failure disappears with an apparent lessening of the pulmonary artery pressure.

Usually a few hours on an automatic pump is all that is required to restore the arterial blood to normal and treat the acute oligopnœa though the tracheotomy may have to be maintained for a few weeks, not only to assist the efficiency of the patient's own ventilation, by reduction of upper respiratory dead space, but also to provide a means of sucking out secretions in patients who are not adequately coughing.

While the patient is anæsthetized and relaxed, any automatic pump in which the frequency and stroke volume can be altered is adequate if a cuffed tracheotomy tube is used. Occasionally a patient-cycled respirator is useful to "boost" ventilation later when the patient recovers consciousness, though it is rarely necessary.

We have had less success in using a patient-cycled positive-pressure respirator in the conscious patient as some American workers have recommended (Sicker and Hickam, 1956)

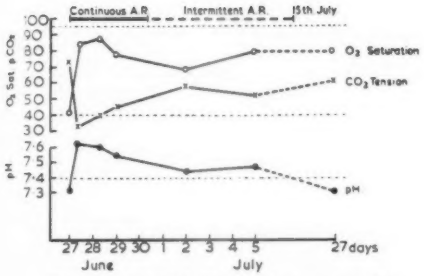



FIG. 1.—Arterial blood changes as the result of treating acute oligopnœa by tracheotomy and mechanical ventilation in a patient with advanced emphysema. (Continuous A.R.—automatic pump ventilation. Intermittent A.R.—patient-cycled ventilation.)

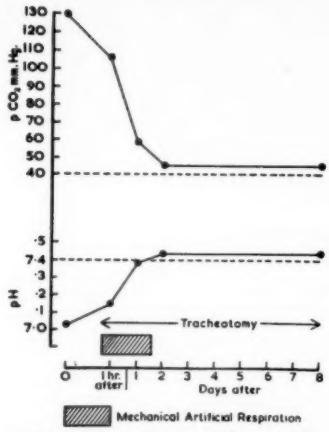



FIG. 2.—Arterial blood during treatment of acute oligopnœa from status asthmaticus.

for we find that oligopnœic patients do not tolerate a mask over their faces and, without a tracheotomy, their stomachs are inflated as well as their lungs! However, tracheotomy is a much simpler procedure than usually considered and really enables an adequate airway to be established. To "take over" a patient's breathing who is severely ill with respiratory failure by artificial ventilation under anæsthesia (when morphine or barbiturates can be given safely) is not only life-saving, but kind to a patient fighting for breath and oxygen.

*Indications for treatment of acute oligopnœa.*—An objection to the treatment of oligopnœa has been that it becomes merely a method of resuscitation of permanent respiratory cripples when it is applied in patients who may have chronic respiratory disease. Like using the artificial kidney in oliguria it is clear that mechanical ventilation with an "artificial lung" should only be undertaken for a temporary and potentially reversible condition. However, it is often extremely hard, if not impossible, to tell which patients have gross and irreversible emphysema when they are seen in oligopnœa from an acute respiratory infection. A demonstration of this is shown by an analysis made by Dr. W. B. Thomson of all the deaths over the last three years at Hammersmith Hospital clinically diagnosed as arising from acute respiratory failure in patients suffering from "emphysema" (Table I). Nearly a quarter had no material degree of emphysema at post-mortem examination, but died from a potentially reversible bronchopneumonia. Three or four years ago we resuscitated moribund patients with gross carbon dioxide narcosis from oligopnœa, who have had the subsequent years of comfortable and useful life.

TABLE I.—DEATHS FROM RESPIRATORY FAILURE IN HAMMERSMITH HOSPITAL

| Year | Nos. dying with diagnosis of bronchitis and/or emphysema | Nos. dying from resp. failure | Pathology: little or no emphysema |
|---|---|---|---|
| 1954 | 26 | 8 | 1 |
| 1955 | 25 | 10 | 3 |
| 1956 | 22 | 9 | 2 |
| Totals | 73 | 27 | 6 |

Thus, we tend to apply methods I have mentioned to all patients in whom there is even a slight prospect of relatively permanent success and then assess their lung function fully, as a guide to prognosis, on their recovery from the acute attack. Fig. 2 shows the progress of another patient who was admitted in status asthmaticus and who, after all the usual treatment had failed, including full steroid therapy, was referred to us by Dr. C. L. Cope. In her case the main problem was removing through the tracheotomy the almost

rubbery exudate which filled her bronchi; even after energetic suction quite a high pump pressure was needed to maintain her ventilation and reverse the severe oligopnœa which had caused such a dramatic change in her arterial blood gas tensions. But she made a complete recovery from this acute attack.

*Treatment of chronic oligopnœa.*—The treatment of mild chronic oligopnœa in emphysema is, like the emergency of acute oligopnœa, another worth-while field of therapeutic endeavour. Occasionally "lazy breathers" can be made to ventilate, with definite improvement in their mental well-being and a probable diminution of their chances of heart-failure from pulmonary hypertension, by the prolonged use of respiratory stimulants, including salicylates. But if such treatment is successful increased breathlessness from excess stimulation of their pulmonary stretch receptors may occur. There is probably a chance that our surgical colleagues could then help such patients by division of the nerve pathways in which these receptors run. But more research into the anatomical pathways of these nerves is much needed.

*Conclusions.*—The use of artificial mechanical ventilation in the ventilatory defects of poliomyelitis, tetanus, &c., is well established. We would like to see the treatment of acute oligopnœa in chronic respiratory disease become equally accepted. It is most rewarding. In fact tracheotomy and mechanical ventilation are rarely needed since energetic use of chemical stimulation of the respiratory centre together with antispasmodics deals with the majority of cases. But the diagnosis of acute oligopnœa must be made and adequate treatment given. We use oxygen in full amounts in all patients who need it and combat any tendency to carbon dioxide narcosis from oligopnœa by appropriate ventilation, achieved either chemically or mechanically.

REFERENCES

DAVIES, H. L., FOWLER, W. S., and LAMBERT, A. H. (1956) *Amer. J. Physiol.*, **187**, 558.
DORNHORST, A. C. (1955) *Lancet*, i, 1185.
FOWLER, W. S. (1954) *J. appl. Physiol.*, **6**, 539.
HUGH-JONES, P. (1952) *Brit. med. J.*, i, 65.
SICKER, H. O., and HICKAM, J. B. (1956) *Medicine, Baltimore*, **35**, 389.

## Mechanisms of Airway Obstruction in Emphysema and Asthma

By E. J. M. CAMPBELL, M.D., Ph.D., M.R.C.P.
*London*

NARROWING of the airways, particularly during expiration, is the most important physiological defect in the asthma, bronchitis, emphysema group of conditions. This expiratory obstruction is responsible for the limited ventilation and total gaseous exchange of which these people are capable. It is also responsible for most of the physical signs and for the reduced performance in such tests as the Maximum Breathing Capacity, Vital Capacity and Forced Expired Volume. The nature of the airway obstruction is poorly understood. The term "bronchospasm" is commonly used to describe it. Although I doubt if many of the people who use the word really believe that spasm of the bronchial muscles is the explanation of the airway narrowing, nevertheless little thought has been given to the number of ways in which the airways may be narrowed. Unfortunately, the common simple ventilatory function tests, although they provide good estimates of the severity of airway obstruction, do not distinguish between the possible causes. The mechanisms may be grouped as follows:

(1) Reversible disease of the airway, e.g. increased bronchoconstrictor tone.
(2) Relatively irreversible disease of the airway, e.g. chronic inflammation.
(3) Loss of elastic support of the airways so that they collapse during expiration.

I want to describe some studies which shed more light on these mechanisms. They were performed on normal subjects, on patients with asthma, and patients with emphysema. A full description of these experiments has been published elsewhere (Campbell, Martin and Riley, 1957), therefore technical details will be omitted.

The basic observation which provided the starting point of this study and which is to be found in earlier work concerns sequence of changes in intrathoracic pressure and rate of air-flow during a forced voluntary expiration (Fig. 1). If intrathoracic pressure is recorded from the œsophagus and rate of air-flow is recorded at the mouth during a forced expiration the rate of air-flow rises to a maximum value and then decreases while the intrathoracic pressure continues to rise. This observation suggested to us that there may be a maximum

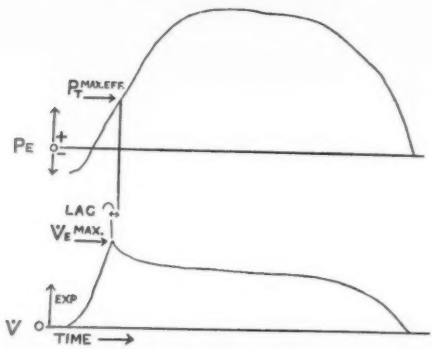



FIG. 1.—Intrathoracic pressure and rate of air-flow during a forced voluntary expiration. $P_E$, œsophageal pressure; $\dot{V}$, rate of air-flow (expiration upwards); $P_T^{MaxEff}$, maximum effective intrathoracic pressure; $\dot{V}_E^{Max}$, maximum expiratory flow rate (*see* text).

effective intrathoracic pressure ($P_T^{ME}$) associated with a maximum expiratory flow rate ($\dot{V}_E^{Max.}$). If $P_T$ rises above $P_T^{ME}$ the airways are narrowed by the high external pressure. This causes a marked increase in resistance and either reduces the flow rate or prevents it exceeding a certain value. We attempted to measure $P_T^{ME}$ and $\dot{V}_E^{Max}$ in 3 normal subjects and in two groups of patients. The first group consisted of 3 patients studied during attacks of asthma. They were chosen because between attacks they had no dyspnœa and had little or no detectable emphysema. The second group consisted of 5 patients with diffuse obstructive emphysema who had long histories of progressive dyspnœa. They were persistently breathless, and were studied after the inhalation of isoprenaline to minimize reversible bronchial narrowing.

In all 3 groups of subjects, in addition to $P_T^{ME}$ and $\dot{V}_E^{Max}$, the air-flow resistance during quiet inspiration was measured, that is to say the pressure difference between the alveoli and the mouth per unit rate of air-flow. This measurement should reflect airway narrowing due to such factors as bronchoconstrictor tone, œdema, &c., but not airway narrowing due to loss of elastic support because the airways are pulled open during inspiration; loss of elastic support only operates during expiration.

Table I gives the values we obtained at resting lung volumes. The maximum expiratory

TABLE I

| Subject | Flow resistance during quiet breathing. (0·5 l./sec.) cm. $H_2O$/l./sec. Mean | Range | Maximum expiratory flow-rate. l./sec. Mean | Range | Maximum effective intrathoracic pressure. cm. $H_2O$ Mean | Range |
|---|---|---|---|---|---|---|
| Normal (3) .. | 1·7 | 1·2– 2·0 | 5·4 | 4·5 –6·4 | 45 | 30–55 |
| Asthma (3) .. | 16·1 | 12·8–17·8 | 0·82 | 0·67–1·00 | 26 | 20–35 |
| Emphysema (5) .. | 6·6 | 3·2–14·7 | 0·96 | 0·58–1·25 | 9 | 3–24 |

flow rate is grossly reduced in both groups of patients to approximately the same levels. There are, however, important differences between the two groups; firstly, the flow resistance is much greater in the patients with asthma than in those with emphysema; secondly, the maximum effective intrathoracic pressure is much higher in the patients with asthma. It appears that in emphysema the flow resistance due to disease of the airways is not grossly increased but the airways become narrowed by relatively low external pressures, and therefore limit the flow rate that can be developed during expiration.

Fig. 2 is a diagrammatic representation of a simple model which can be used to study the factors affecting the patency of the airways during expiration. A mathematical analysis based on this model leads to conclusions consistent with our experimental findings. In Fig. 2 the airways have been represented as being in two stages, a proximal one whose walls have high rigidity and a distal one whose walls have negligible rigidity. The intrathoracic pressure is $P_TD$, the alveolar pressure is $P_{Alv}$ and the pressure in the lumen of the distal airway close to the junction with the proximal portion is $P_L$. It is assumed that an expiratory force

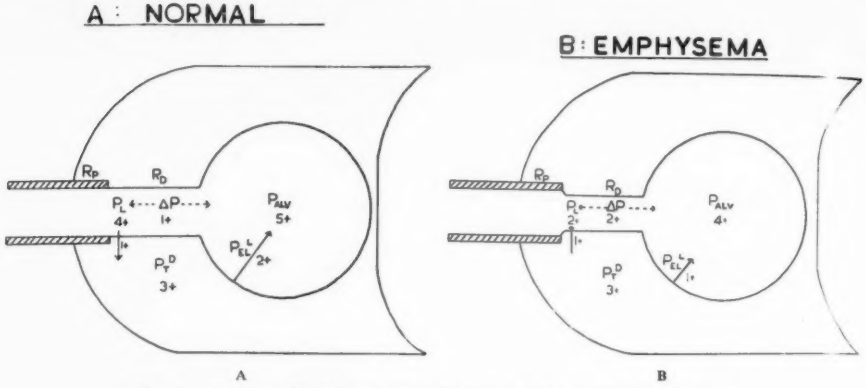



FIG. 2.—Factors affecting patency of airways during expiration (*see* text).

such as that provided by the contraction of muscles of expiration has raised $P_TD$ to 3+ above atmospheric. Fig. 2A represents a normal lung in which the elastic recoil ($P_{EL}L$) increases the pressure within the alveolus by 2+. Alveolar pressure ($P_{Alv}$) therefore $=P_TD+P_{EL}L=(3+)+(2+)=5+$. In Fig. 2B which represents an emphysematous lung the elastic recoil is only 1+ and $P_{Alv}=P_TD+P_{EL}L=(3+)+(1+)=4+$.

If in the normal lung the resistance in the distal airway is so small that the pressure drop ($\triangle P$) from the alveolar space is only 1+, then $P_L=P_{Alv}-\triangle P=(5+)-(1+)=4+$. The pressure difference across the wall of the airway is therefore $P_L-P_TD=(4+)-(3+)=1+$. In the emphysematous lung more resistance in the distal airway is assumed so that $\triangle P=2+$, and $P_L=P_{Alv}-\triangle P=(4+)-(2+)=2+$. In these circumstances the pressure difference across the wall of the airway is $P_L-P_TD=(2+)-(3+)=1-$. This is the same as a pressure difference of 1+ tending to narrow the airway.

If one neglects additional pressure effects caused by the properties of the wall of the airway itself, the pressure difference across the wall of the normal airway will cause it to remain open whereas in the emphysematous lung it will cause narrowing.

The mechanisms responsible for the expiratory obstruction in asthma will not be discussed partly because the possibilities are more complex and partly because my main aim is to suggest a method of approach to these problems rather than to present a complete analysis.

In spite of the initial impression of complexity this approach does suggest that much greater discrimination between mechanisms of airway obstruction is feasible.

ACKNOWLEDGMENTS

I am grateful to the Editors of the *Bulletin of the Johns Hopkins Hospital* (Campbell *et al.*, 1957) for permission to reproduce some of the material used in this communication.

REFERENCE

CAMPBELL, E. J. M., MARTIN, H. B., and RILEY, R. L. (1957) *Bull. Johns Hopk. Hosp.*, **101**, 329.

# Section of General Practice

President—G. M. KERR, M.B., L.R.C.P., F.F.A.R.C.S.

[*November* 20, 1957]

## DISCUSSION: THE MANAGEMENT OF THE HOPELESS CASE

**Dr. Ronald Gibson** (Winchester):

I am told that in ancient Babylon it was against the law for doctors to attempt to treat hopeless cases. To-day, as I offer a twentieth century family doctor's conception of the management of these cases, I view with some envy the position of my Babylonian predecessor.

"Hopeless" patients are those of any age group who are suffering from a disease or state which we, with our present knowledge, regard as incurable. At any moment, with increasing knowledge, one or more will be struck off the list. In other words, the incurability or hopelessness is used by us as an expedient pending further research, and there is no reason therefore, why we should not adopt a positive approach to those patients from the very beginning, and follow the excellent example of the Bishop of Durham (Harland, 1957) who said of the dying that they must never be deprived of their last joy on earth—which is hope.

Hope is a state of mind in which one expects confidently that what one desires will come about—it is confident anticipation. Until a certain stage is reached in the lives of these patients for whom we have so far failed to find a cure they are confident of their return to a state of health comparable to that of the average individual they see around them. They are, in fact, hopeful. When they begin to die their desires change, so that they look forward with confidence to their dying and to this world's release from their adversities. They are still hopeful.

This approach, of course, could be called academic and unreal. But I must emphasize at the outset that the theme of care (so far as I am concerned) must be played in a major key of which the dominant note is hope. The basic principle is that the patient's expectation, whether of life or death, must be created by the doctor, nurtured and maintained by him, and guided by him so that hopelessness (whilst it may conveniently appear as the title of this debate) never enters the patient's mind.

To pigeon-hole or catalogue these cases would, or course, take a book in itself. Hopelessness may be diagnosed at birth or at any time within the next hundred years. Care may extend over hours, days, months or years. So that some limiting definition is necessary.

### DEFINITION

I. Gavey (1952) says that the term "hopeless" implies that the patient suffers from "a disease or state from which recovery is beyond reasonable expectation". This classification could be broken down, I think, by dividing such cases into two:

(1) Those whose expectation of life has been materially diminished by reason of the disease from which they suffer, and

(2) Those who, whilst suffering from a disease or state from which recovery is beyond reasonable hope, will not suffer any diminution of their expectation of life because of it.

Having defined hopelessness I must now explain what I mean by "care".

II. Care implies *total* care, that is to say I am looking upon the patient as suffering from more than just a specific illness. I am acknowledging that chronic illness (as Jerome Tobis (1955) emphasizes) has a social as well as a biological character, and therefore the efforts of the doctor and his helpers must be directed towards the maximum function of the patient in all fields—physical, psychological, vocational and social. I acknowledge, too, that this is no easy task—for care must not continue for a limited period and then be allowed to lapse because of diminishing interest, lack of new ideas, or over-work. Care that is allowed to regress is worse than no care at all.

How does care begin? How is the degree of care assessed? Obviously the first factor to be considered is the disease from which the patient is suffering, into which category it falls and the degree of disablement it is causing. Symptomatic treatment can then be instituted. This is care of the disease and not of the patient—the latter will follow.

Starting in this way the doctor gets to know his patient, the patient's family and his environment, and he can arrange all three into the pattern that he knows will be most suitable for the long time ahead.

I propose, therefore, to start with the care of the environment, to proceed from there to care of the relatives, and then to care of the patient.

### The Environment

The design of the environment depends on two major factors at the outset: the home background and the financial status. The Welfare State has influenced both of these.

In the first place it has raised the standard of living of the population, eliminated gross poverty and improved public health education. Thus the State doctor, under the National Health Service, can enter practically every home in the country, and can take with him the State nurse, the health visitor, the home help, the social or welfare worker, without any thought for the family's income in pounds, shillings and pence.

Nowadays the degree to which these people can influence the environment, therefore, depends more on whether the patient is surrounded by a loving and responsible family than upon the financial or social status of the family, and it is unfortunate that the State, in taking so much obligation upon itself for the welfare of society has, at the same time and inevitably, lessened individual responsibility towards the family. Without this individual responsibility even a healthy family may break down, and it is certain that one which includes a chronic sick person will tend to push the responsibility for care and management on to the State, and the patient's environment will be that of a chronic sick hospital or nursing home.

Attention to environment obviously involves in the first place a rearrangement of the house—not always easy to bring about at once—often a great deal of suggestion is required over a long period. A bed-room downstairs may mean considerable sacrifice to some families; with others there will be room to spare. Some patients—particularly the older ones—fear the ground floor at night.

Such a move may also necessitate the provision of lavatory accommodation downstairs, the elimination of steps in and outside the house, the widening of doors and gates, and so on. In this re-educating and conditioning process the health visitor can be a great help to the doctor, and also in introducing the Daily Living Department to the family.

There is, unfortunately, no time to enlarge on the work of this department. So many "gadgets" can be invented and provided. Suffice it to say that almost any individual's needs can be supplied.

The environment plays an important part in building up the pattern of the patient's day – not only to keep him amused and occupied in gainful occupation, but also to impress him continually with the true fact that he can still be a useful member of the community.

Diversionary activities designed to take the patient's mind off himself and his illness include the television and wireless, cross-word and jig-saw puzzles and various card games; the encouragement of hobbies, such as carpentry, painting and needlework, writing and stamp collecting. All these fall within the province of the social and welfare workers, the W.V.S. and the Red Cross. Not to be forgotten also are visits from the librarian and, perhaps most important of all, the arrangements which must be made for continuing the patient's education, particularly along the lines necessary for possible re-employment. Thus it can be seen that *people* play a prominent part in the make-up of the environment. Dr. Alfred Worcester (1935), for example, reminds us of the importance of introducing new friends to the patient, of ensuring his association with young people and of maintaining at all costs his personal vanity.

### The Relatives

To turn to the relatives. I am reminded of the young general practitioner who, after a misdiagnosis and subsequent death of his patient, felt it incumbent upon himself to apologize to the relatives for his shortcomings. They were quick to reassure him. He was, they said, the only one who had given them any hope.

Where possible it should be left to the family doctor to deal with relatives. This is not intended as a slur on the consultant; I always pity him when he has to interview relatives in hospital—he has probably only known the patient for a few hours, and he meets the relatives face to face for the first time outside the ward. How can he possibly know how to arrange his story—how much to tell and how much to leave out—and, particularly, how much of the future to predict? We have to deal with two types: those who are suddenly faced with an acute crisis—such as the onset of poliomyelitis in a child; or those whose lives have been gradually conditioned to a change in the family environment—such as would be brought about by the progress of an inoperable carcinoma in an elderly and dependent relative. The latter change, being slower in development, is more easy to manœuvre, but both groups depend for their management on the personality and outlook of the particular relatives, and it is impossible to assess this at a first meeting.

It is, therefore, the G.P. with a knowledge of the family extending over years, who best knows how to manage these people. Mismanagement of relatives means mismanagement of patient, for the hopeless case is going to be far more dependent on them than on the doctor or his helpers—it is therefore vital that the right outlook should be adopted from the start.

Recently, a patient told me, quite calmly, that she had had her eyes tested and had been

told to go home and learn braille, for within two years she would be blind. I winced at the abruptness of this but she seemed quite contented and determined to make the most of her environment for as long as she could see it (she was already making a note of things she had never seen before, and storing them up so that she would remember them when she could no longer see them). Not so her relatives. They had been given an even blunter prognosis. Their lives were going to be changed by this failing vision to a greater extent than the patient's, for it is one thing to go blind and another to have to care for the blind—and for an indefinite period. A patient going blind is, after all, a hopeless case according to our definition, although the expectation of life may not be diminished, and this is *not* the way that the family doctor would choose to set about preparing patients and relatives for a changing scene.

One talks of dependence of patients on relatives. If anything a more tragic situation develops when relatives become dependent on patients. The progress of a chronic illness may bring with it the development of a selfish or possessive attitude on the part of the patient towards those in closest contact with him. The family doctor must watch out for this and do all he can to stamp on it before it becomes irreversible. I remember one devoted family, all of whom were wage-earners until one sister developed Parkinson's disease. Another sister stayed at home to look after her whilst the remaining two sisters and one brother continued to maintain the family exchequer. It was all done with the best possible intentions. Now the one sister is irretrievably bound to the invalid who "cannot live without her", and every bit of strength is being sapped out of her as the years and the disease proceed very slowly to take their toll of the patient. Care of a hopelessly sick person is also the responsibility of the family as a whole and must never be delegated to one individual member of it.

If it takes an experienced G.P. to lead relatives into the atmosphere of chronic sickness without undue trauma to themselves or to the patient, it requires even greater tact and knowledge to guide them through the phase when a hopeless life gradually proceeds towards its end. It is difficult to understand that those who immediately care for a chronic patient may become so attached to him that they will struggle against the only possible and, indeed, only happy conclusion. This struggle can be dangerous because it may be transmitted to the patient, and what might have been a tranquil ending to a life becomes one of bitter argument right up to the last; it may lead to resentment against the doctor, his helpers and family friends, to the employment of all sorts of unorthodox methods of treatment and even, finally, to a turning away from the God who allowed death to separate them from their loved ones.

## The Patient

We have now discussed the inauguration and supervision of the programme which is to absorb those who make up the most intimate circle around the patient—the supporting cast, as it were. We have arranged the environment to suit the particular patient—in other words, the scene is set. We must proceed to a consideration of the management of the patient himself—the leading actor.

I am convinced that from the very outset it is the family doctor's duty to encourage the patient in an aggressive attitude to his disease. Such an approach has, in fact, been emphasized recently by Dr. Bodley Scott (1957) who, in an address to the B.M.A., said that the patient's happiness is best served by encouraging him in an aggressive attitude towards his disease—to keep at work and to live a normal life until physical disability makes it impossible. Along with this, as Dr. Bodley Scott says, must obviously go the exploitation of every available means to procure even temporary and partial remission of the disease. Both of these—the aggressive attitude and the attempts at treatment—are calculated to encourage the patient to a positive attitude towards his illness—in other words, a hopeful attitude.

The essence is that the onset and progress of a disease must never be permitted to interfere with the patient's love of life. He may love it from a bed or a chair, a bedroom or a ward, but the changing circumstances of his life must not interfere with his devotion to it. Tolstoy (1868–69), it will be remembered, said that the most difficult thing—but an essential one—is to love life. To love it even while one suffers, because life is all.

Which leads me to my next point: I have often found it useful to remind newly diagnosed hopeless patients that, if they come to think of it, life is always a struggle—even for the apparently healthy individual, and either mentally, physically, or both. The onset of an incurable disease may add to the struggle but, even so, may not bring it up to the level of that suffered by some people who, though apparently healthy, yet are constantly fighting some unseen physical or mental disability which they dare not share with anyone.

The onset of care, then, or the first phase of care, revolves round an assessment of the personality of the patient and of his ability to tackle the future; helping him in the first few weeks to recover (or, if possible, to enhance) his love for life and his determination to go on living; enabling him quietly to settle down in his new environment and to accept his relatives, the doctor and his co-workers in their new status; and, finally to start him unobtrusively on the routine of his new daily existence.

### The Routine of Daily Existence

It is this "routine of his new daily existence" with which we are now concerned. Obviously it would be impossible to detail the whole list of apparently hopeless cases in order to outline the specific treatment for each. I am going to concentrate, therefore, on what I call "average" care, which is really the build-up of care ready and waiting for all new hopeless cases, one or other end of which may have to be modified to suit a particular case. When first discharged from hospital and waiting for the family doctor to call the patient will nearly always remain in bed. Even though he has been up every day in hospital he will keep to his bed at home until the G.P. confirms that he is the same patient suffering from the same disease, and therefore, liable to the same treatment at home as in hospital. Rather like a ship that has been prepared for launching he remains unmoving until the home doctor presses the switch!

This is not altogether a bad thing, because the first visit must include a preliminary chat. Even though he has been in hospital there will be a lot he still requires to know. Everything possible must be carefully explained to him with mingled sympathy and honesty, and then he must be told of what has been arranged for him at home and of how he is expected to proceed. A word of warning here: he may not have been told of the hopelessness of his case. It is disastrous for the family doctor to assume that the patient has accepted that he is suffering from an incurable disease when, in fact, for one reason or another, he has been carrying on under the assumption that he is going to get better. The contrary is, of course, equally true—when the patient has prepared himself for the inevitability of his future and the family doctor optimistically starts off on the lines that no effort will be spared to get him better. Both can happen if the first talk is not carefully guided and controlled by the doctor.

### Physiotherapy

When possible, then, the activation of the patient proceeds from the first visit of the doctor, bed-rest being carefully balanced against over-exertion. With this goes the arrangement and management of exercises, requiring the active participation of the patient and having the additional advantage of helping to take up a good part of his day. Additional aids and self-help devices come in here, and physical rehabilitation may have to include the advice and assistance of various specialists—the specialist in physical medicine, the orthopædic specialist, the neurosurgeon and the plastic surgeon—all working with the family doctor towards the three major aims described by Jerome Tobis (1955): the relief of pain, the increase in range of motion and the increase in motor power. It is the G.P. in the first place who must recognize the need for the appropriate specialist, and call on him.

### Chemotherapy

Chemotherapy (or treatment by drugs) clearly has an important place in average care—if only for the mouth, the bowels, the skin, for pain and for sleep—apart from any specific treatment.

As an analgesic I still use the pot. bromide and aspirin mixture[1] I used in hospital, with or without the addition of codeine phosphate (omitting any reference to possible constipation with the exhibition of codeine!). Largactil, Physeptone and pethidine follow in that order. I find Largactil an immensely useful drug, especially for the vertigo and/or nausea of the senescent. For sleep, "Mist three fifteens,"[2] Soneryl, "Spansules" of phenobarbitone and Omnopon furnish all I need to ask, and here I must say that I cannot subscribe to those who write of the necessity for increasing doses of morphia in treating the dying. I have never had to resort to this.

For the skin, in addition to the nurse's routine care, Compericum has a definite place, and when the skin breaks down I always first use an ointment[3] to be found in the St. Mary's Hospital Pharmacopœia—I know it must be good because of the number of nurses who insist on using it.

I find that constipation usually responds, at any rate in the first place, to a compound paraffin emulsion night and morning, with or without the addition of liquid cascara in varying amounts to the evening dose. Mist. magnes. hydroxidi with liquid paraffin is also useful, and I find Senokot of great value.

Urinary and fæcal incontinence are distressing complications and between them are more likely than almost anything else to cause the breakdown of home care (except, possibly, insomnia and the constant need for care at night). In treating these one has to rely on good

[1]Pot. bromid. 7½ grains, codein. phosphat. ⅛ grain, mist. ac. acetylsalicyl. *ad* ½ ounce.
[2]Tinct. opii 15 minims, pot. bromid. 15 grains, chloral. hydrat. 15 grains, aqua *ad* 1 ounce.
[3]Acidi borici 15 grains, olei eucalypti 15 minims, bismuthi subnitratis 60 grains, zinci oxidi 1·0 grains, oleum ricini *ad* 1 ounce.

nursing discipline combined with regular habits, encouragement and the application of almost eternal patience.

There is so much more to chemotherapy than I have either the time or the expert knowledge to include.

### Diet

Over-eating must not be encouraged, but, on the other hand, so many patients, particularly the elderly, have such poor appetites that there is little hope of correcting metabolic deviations and it does seem that no amount of vitamins, calcium, androgens and/or œstrogens can overcome the defect. No harm can come from giving in to particular cravings, and there is no point in forcing a patient to eat food he heartily dislikes simply because the relatives think it is good for him. I have found Cytamen, Becosym and Complan useful adjuncts.

### Social Therapy

I have already discussed this fairly fully under "the environment".

The social worker is an invaluable member of the doctor's team. It is beyond the time, and, I imagine, the ability of the average family doctor to analyse the vocational capabilities of the patient, the capacity for further education or for a return to some form of employment. The analysis *must* be made, for it will be remembered that we must impress the patient with his continued importance to the community at one level or another.

Work need not necessarily be for financial gain. It may merely be for mental relaxation; as a time-passer or (perhaps most important of all) as a means of doing service to others in the community.

### Spiritual Therapy

It has always seemed remarkable to me that most patients automatically regard their doctors as atheists or, at best, as agnostics. Many times I have regretted that a patient should feel it necessary to apologize to me for the suggestion that he might get some help from a priest—and would I mind if he tried. Worse still is the surreptitious consultation between patient and parson without letting the doctor know, in case he would be offended or would not understand.

I include spiritual therapy automatically in my care of the hopeless case, and only if I receive a dogmatic refusal of such help do I pass over it. By this I do not mean that I encourage the patient to consult *any* clergyman. If he definitely states that he would like to see a particular one I ask if I may contact him. With this permission I tell the parson the medical aspects of the case and ask for his co-operation.

If I am *not* specifically asked for a particular priest I must say that I prefer my own choice. Where I come from, of course, they can be seen wandering about in prides, and it is not difficult to find one to help in almost any situation; but I have learned that, like specialists in other fields, each tends to show a partiality for a particular type of patient. I need not say how much nicer it is to be able to call in the parish priest, since he exercises the same authority in the spiritual field as the family doctor does in the medical, but it is not always possible.

I am convinced that a patient on whom it is not possible to apply spiritual therapy is missing a major part of his treatment, and the lack of this vital constituent of total care makes the remainder far more difficult to apply and far less effective in result.

One cannot leave this aspect of care without touching on the tragic move so often made by patients or their relatives who, as I have already said, in desperation at the hopelessly inevitable nature of the prognosis, proceed to employ some peculiar and unorthodox "spiritual aid", of which there are so many different varieties. That some of these so-called spiritual healers, or the like, are honest in their beliefs and in their desire to help there can be no doubt, but others merely exist in order to play on the feelings of, and to make money out of, the hopelessly ill. All one can do is to wait for the anti-climax and, when it comes (as it inevitably must) receive the patient back into the fold without recrimination. Argument in the beginning or recrimination at the end may bring about a change of doctor, and with this a possible change in the routine of daily life and of treatment. This should be avoided at all costs (even that of the doctor's pride) for enough damage may well have been done without this additional risk.

### Psychotherapy

This undoubtedly has a place in the care of the hopelessly sick. I am still middle-aged enough as a family doctor to believe that, other than in exceptional circumstances, I ought to be able to manage my hopelessly sick patients as though psychiatrists had never been invented. I hope that too many of my patients have not suffered for my obsession in this respect although, even so, I fear that I should remain unrepentant.

### The Phase of Dying

In the care of the patient when dying, all these therapies still have their place. Gradually chemotherapy and spiritual therapy will take precedence over the others. The fundamental aims at this stage are the banishment of pain and anxiety. A judgment of the patient's personality and beliefs must sway the doctor in his decision as to when, if at all, the patient is to be told that the last stage has been reached, and how to tell him; often the priest can and should do this last sad office.

We all of us know how peaceful death can be when it is faced without fear, and equally how delicately the process of dying must be handled by all concerned so that nothing is allowed to ruffle the calm or break the stillness. William Hunter said "How easy and pleasant a thing it is to die"—and this is true.

Once Sir William Osler was visiting a dying child and knowing that the end was near he picked a beautiful red rose from his garden. He took it out of his pocket in the sick room and told how he had watched the last rose of summer growing in his garden and how the rose had called out to him as he passed by, saying that she wished to go along with him to see his "little lassie". The little girl understood that neither fairies nor people could always have the colour of a red rose in their cheeks, nor stay as long as they wanted in one place.

Death is not a hopeless thing; nor are the dying without hope. Therefore, if for no other reasons, our care of these patients is infinitely worth while.

### REFERENCES


Gavey, C. J. (1952) The Management of the "Hopeless Case." London.

Harland, M. H. (1957) *Brit. med. J.*, ii, 287.

Scott, R. B. (1957) *Brit. med. J.*, ii, 287.

Tobis, J. S. (1955) *J. chron. Dis.*, **4**, 164.

Tolstoy, L. (1868–69) War and Peace. Moscow.

Worcester, A. (1935) The Care of the Aged, the Dying and the Dead. Springfield, Ill.


**Dr. C. J. Gavey** (London):

There is a growing medical and lay interest in the problem of the hopeless case. I tried to assess the situation in 1950 (Gavey, 1952) when I was struck by the paucity of literature of a type that was readily available; but since then statements have been made in other Sections of this Society, notably in the Section of Medicine on "The Management of Advanced Cancer" (1955) and in the Section of Surgery on "Palliation in Cancer" (1955): Medical books have appeared such as "Should the Patient Know the Truth" edited by Standard and Nathan of New York (1955) and very recently Davidson's "Medical Ethics" (1957) containing contributions pertinent to our subject. Laymen have also written of their experiences as sufferers from dread diseases, e.g. Evans (1952) from epilepsy, Opie (1957) on poliomyelitis and Hession (1956) on cancer of the colon with colostomy, to mention only a few. Last year the Archbishop of Canterbury collated data on Divine Healing (1956).

Television has given a great deal of information to the general public as to what can be done for cancer and certain types of heart disease, and we cannot stop thirst for knowledge on these matters. What is happening in America is more slowly happening here. I mean the study of the facts of disease by all and sundry. A degree of impatience is appearing in people who want to know the why and wherefore, and up to a point they have a right to this information. In other words they can read and learn of the scientific aspects of medicine; but its method of application rests on a higher plane and requires the long arduous training of a doctor who must retain independence if his best is going to be good. At no time has the doctor's prestige been so much in the balance, but we need have no fears if we give judgment based not only on knowledge but also on feeling. Judgment is difficult and increasing knowledge brings its own problems: a hundred ways of investigation bring a hundred ways of going wrong, hence the need for a balanced attitude to investigation, in teaching and in practice, based on the highest integrity, and a profound respect and awe for body and soul. Sherrington (1951) in "Man on his Nature" put it to us that "human doings, human feelings, human hopes and fears move man as does nothing that is not human . . . We have, because human, an inalienable prerogative of responsibility which we cannot devolve, no, not as once was thought, even upon the stars. We can share it only with each other". Science, wonderful though it is nowadays, and worthy of meticulous attention, provides no short cuts to assessment of the patient as a whole; this can only be achieved by careful study at the bedside as of old. Graves once said "Genius will not compensate for lack of clinical study at the bedside".

Laymen are gradually acquiring a knowledge of survival rates instead of death-rates and

it is proper that it should be so, for anyone who is stricken with a killing disease will tend to think of the possibility of recovery rather than the inevitability of death and so from the start a valuable defence is set up. Initial fears from increased knowledge are giving way to the feeling that something substantial can be done. Have I a chance? says the patient. In order to be able to answer this with the confidence that the patient can detect, we should have in mind the cures or arrests that we have known. Men will fight against great odds, but not for so long if defeat is thought to be certain. Thus the patient, now better informed, plays an increasing part in the management of his disease but at the same time our responsibility becomes infinitely more exacting.

Certain *religious considerations* are relevant to our work as doctors. When the situation seems hopeless, nothing remains to solace except Faith, but Faith can be like a ". . . promontory of the sea, against which, though the waves beat continually, yet both itself stands and about it are those swelling waves stilled and quieted" (Marcus Aurelius). Most patients are not afraid of death but are reluctant to die. I think that applies to some atheists and to religious folk alike. The reluctance to die has largely to do with the welfare of remaining relatives and the instinctive will to live. In this country it is now seldom that we meet patients who dread death because of possible utter damnation hereafter but perhaps the majority have qualms at some time about their position in after-life, and would welcome an opportunity of improving at the last their relationship with God. Though we would wish that all had given this communion with God a life-long application, it is not practical to assume that. My view is that the doctor is not expected to minister himself but he is expected to see that spiritual help is available and to co-operate readily with the priest. Though there is a growing mutual respect, I think it is common for the clergy to be reluctant to approach the doctor, and the doctor the clergy. Then the help of an intermediate person, the Sister in hospital, or a friend or relative in general practice, is appropriate and welcome to all parties. It is very doubtful whether anyone should be allowed to die of chronic disease without some warning of that possibility, at least at the very end. We know that Roman Catholics have unwavering views on the utter necessity of preparing a patient for death and anyone with religious feeling would I think desire everyone to be prepared; but as doctors we have no prerogative to decide this issue categorically, but simply to co-operate wholeheartedly with the clergy in satisfying the needs of our patient. I would emphasize here that the last Sacrament does *not* remove all hope. It is for those in *danger* of death, not necessarily of certain death. In regard to the patient who is actually dying, I believe he is more often aware of the ministrations at the last, than the doctor might think on medical grounds. A doctor is recognized as one who is unbiased as to race or creed, which is perhaps the reason for the common unjust accusation that doctors are lukewarm in matters spiritual. Indeed many, possibly most, doctors rely consciously on religious beliefs as a source of strength in their arduous work.

Courage is a virtue with which we are very variously endowed and we must recall that disease may in some cases undermine courage by reason of its nature or severity, especially when prolonged, and associated with distress in the family. Let us remember the experience of our Lord: "He was withdrawn from them a stone's cast and kneeled down and prayed: 'Father, if thou be willing, remove this cup from me: nevertheless not my will, but thine be done.' "

*Telling the patient.*—The Hippocratic Oath charged us to "follow that system or regimen which according to our ability and judgment, we consider to be for the benefit of our patients and to abstain from whatever is deleterious or mischievous". In the doctor-patient relationship the patient has implicitly charged the doctor to give him the maximum help in combating the disease, and as we doctors see it, the patient has in his own interest, implicitly left this problem of telling to the doctor's judgment. It is a human right to know the truth about oneself, if the truth be known, but it is not incumbent on anyone necessarily to exercise that right. Most doctors say that for themselves they would wish to know the truth, e.g. Osler, Cushing and others. The doctor must be sure of his facts yet prognosis is difficult and full of pitfalls. The slightest doubt regarding diagnosis and prognosis will indicate the postponement, if possible, of intimation of the state of affairs until time has clarified the position medically, and prepared the patient for bad news. All of us could quote examples of mistaken prognoses, but if only we remain aware of our fallibility we are not likely to do harm in this connexion, especially if, when telling our patients, we include what we don't know. More patients would seek the truth if they realized that terminal illness is not as a rule attended by acute suffering. In most diseases a toxæmia supervenes which dulls the mind and favours a peaceful exit. More patients would ask if they had the opportunity, hence the importance of regular visiting. Some do not want to know the disease at work—simply their expectation of life. Others only want the sympathetic ear of a responsible person. A relative should know the position. It is not infrequent for the relative to ask that the patient be not told. This may be reasonable but our prime duty is to the patient.

The patient who obviously knows the truth may never seek to talk about it and a mutual understanding rests on this. There is the occasional patient, rare in my experience, whom one feels should not be told lest the truth harries him and his family. The maxim to do no harm applies here, but it is usually possible to advise against undertaking important commitments simply on grounds of ill-health. Self-deception is sometimes fostered and it might be unwise to intrude at that moment unless some important family or public interest demands attention to his affairs. There is something to be said for the method of telling whereby a relative or close friend takes that responsibility for as Munk (1887) said "they do so without destroying his hopes, for the patient will still believe that he has an appeal to his physician beyond their fears".

Perhaps half the population still believe that we usually avoid the truth. A few venerable physicians and surgeons have told no one of a fatal issue if they could possibly avoid it. I have told many and never regretted it, but I have tempered the truth with such solace as I could muster, never closing the door until the very end, for as Ogilvie (1957) has said: optimism is the greatest analgesic and hope is the most certain tranquillizer. In a patient with cancer for instance, it may greatly facilitate treatment if he knows the rationale of it but once the position has been stated there is no place for reiteration. I have known some who, having known the truth did not finally accept it and thus they found strength to go through their treatment. Mystery, fear of the unknown, may sap the patient's strength and undermine his morale. I have not met an example of suicide in a patient whom I have told, but I know that very rarely it does occur.

I would say without hesitation after years of study of this problem that there is more to be gained than lost by adopting the attitude that enough should be said to satisfy those who would wish to know the truth. Much depends of course upon the way and time of telling, but I have been astonished at the courage, determination and final resignation of so many patients and my admiration and thankfulness for their fortitude grow daily. The fact remains that there are still two attitudes to be found among us. Those who tend to tell and those who tend not to tell. I feel that the tide is turning in favour of telling, and that this is the line I take with students whose task will be greater than ours, but I am not suggesting that late in his professional life a doctor should necessarily change his attitude in favour of telling if he has not been wont to do so, for the path is indeed rocky and tortuous and he may falter to the detriment of his patient.

Dr. Ferriar, the old physician (quoted by Munk, 1887) said: "The physician will not torment his patient with unavailing attempts to stimulate the dissolving system, from the idle vanity of prolonging the flutter of the pulse for a few more vibrations; if he cannot alleviate his situation, he will protect his patient against every suffering which has not been attached to it by nature."

## REFERENCES


Archbishops' Commission (1956) Divine Healing, *Brit. med. J.*, , Supp. 269.

DAVIDSON, M. (1957) Medical Ethics. London.

EVANS, M. (1952) A Ray of Darkness. London.

GAVEY, C. J. (1952) The Management of the Hopeless Case. London.

HESSION, B. (1956) Determined to Live. London.

MUNK, W. (1887) Euthanasia. London; pp. 29, 87.

Management of Advanced Cancer (1955) *Proc. R. Soc. Med.*, **48**, 373.

OGILVIE, H. (1957) *Practitioner*, **179**, 584.

OPIE, J. (1957) Over My Dead Body. London.

Palliation in Cancer (1955) *Proc. R. Soc. Med.*, **48**, 703.

SHERRINGTON, C. (1951) Man on His Nature. 2nd edit. Cambridge; pp. 293, 294.

STANDARD, S., and NATHAN, H., eds. (1955) Should the Patient Know the Truth. New York.

# Section of Radiology

President—E. DUFF GRAY, M.A., M.D.

[*October* 18, 1957]

## The Present Role of Surgery in Carcinoma of the Breast [*Précis*]

By E. STANLEY LEE, M.S., F.R.C.S.

*London*

THERE are two approaches to this problem: to look at the disease as an entity, and try to evaluate different methods of treatment relative to the whole; or to select a treatment, such as radical mastectomy, and try to identify a group of cases in which this method gives satisfactory results.

In either case, certain well-known difficulties make valid conclusions hard to reach. These difficulties, big enough within a single series, but much greater when different centres or series have to be compared, include the following:

Firstly, the notorious difficulties of precise clinical staging; largely due to the inexactness of clinical observation and description.

Secondly, the slow tempo of the disease, which makes assessment of results a very slow process; and, because techniques, observers and material are continually changing, makes comparison of any group of cases with a previous group—even at the same centre—fallacious.

Thirdly, our incomplete knowledge of the natural history of the disease; for instance, we do not know if the demonstration of *microscopic* metastases by biopsy invariably means future *clinical* dissemination of the disease.

Even if we could accurately assess the probability of occult general spread in a given case, there would still remain the ethical problem as to how high this probability must be before we abandon "radical" for "symptomatic" treatment.

In the palliative or symptomatic categories, surgery may still play a part in preventing or reducing local symptoms, but each case must be judged individually and surgery is but a small facet of treatment.

In the "curable" categories, the stakes are higher and choice of treatment accordingly more crucial. The choice may lie anywhere between two extremes: minimal surgery designed merely to simplify radiotherapy, and extended radical procedures such as those of Urban or Wangensteen. Experience is, however, tending to show that involvement of mediastinal nodes is indicative of general spread and contra-indicates radical surgery. Pending the emergence of reliable figures, a sensible compromise seems to be to remove surgically what is reasonably accessible, thus enabling the radiotherapist to concentrate his whole effort on the remaining areas. Records show that, where the primary is small and without gross signs of local infiltration, and the axillary involvement is nil or early, local recurrence after radical mastectomy is rare. In these cases, therefore, radiotherapy may be confined to the supraclavicular and internal mammary areas giving them a really satisfactory sterilizing dose in the hope of still further increasing the rate of cure.

# The Comparison of Two Radiotherapy Techniques in Breast Carcinoma [*Abridged*]

By R. W. Gunderson, F.R.C.S., F.F.R.
*Portsmouth*

It has been customary to treat carcinoma of the breast post-operatively, with a tumour dose of 2,000–4,000 r in two to four weeks and this is still widely practised. Since October 1949, the techniques advocated by Baclesse and Lenz using a higher dosage over a longer overall time have been used in Portsmouth.

The first groups of cases were treated prior to this time under the ægis of A. G. C. Taylor of Southampton to whom I am indebted for permission to include them.

An analysis of the very varied dose-time factors used by Baclesse in treating laryngeal carcinoma did not reveal any clear optimum. The mean dose of 5,500 r given in a mean time of eight weeks, modified a little with growing experience, has been used in the second group. The internal mammary chain was also included in this group, whereas in the short course series only the chest wall, axilla and supraclavicular areas were covered.

It is only fair to say that 28 patients who had a genuine simple mastectomy subsequent to October 1949 were included in the short course though only one of these fell into Stage IV. Any bias therefore is in favour of the shorter treatments. Otherwise all patients seen subsequent to October 1949 are included in the ten-week course whether they had radical treatment or not. By general agreement with the surgeons Stage I patients without glandular involvement histologically were not given irradiation and are excluded from the figures presented. Those having recurrent carcinoma when first seen are excluded from both series. Stage I patients are therefore made up of those with glandular involvement on histological examination, and a few patients with growths in the inner quadrants or close to the edge of the breast, where the surgeons concerned felt their prognosis might be helped by irradiation.

## Staging

Manchester Staging has been used throughout. As Stage I were treated by operation only, these had to be a little more strictly defined, otherwise a 70–85% five-year survival could not be expected. Tumours tethered to pectoralis major were relegated to Stage III as were those which were large in relation to the size of the breast. Haagensen and Stout (1951) have shown that the prognosis in larger tumours is a good deal worse, and put the upper limit for Stage I at 6 cm., while Ducuing, Tailhefer, and Baclesse (1948) put it as low as 3 cm. McWhirter, with less strict criteria, has a 60% five-year survival in the Stage quoted for him.

The distribution by stage in each group is a little different, there being only 16% of Stage I cases in the long course as opposed to 27% in the short. Patients not receiving radical therapy constituted 27% of the short course but only 16% of the long. The main reason for this lies in those judged too ill or too old. Failure to complete treatment and the presence of distant metastases affect each group identically.

As the surgeons became more familiar with the relatively mild reactions, pre-operative irradiation was tried in some late cases. A photograph of a patient in Stage III who had a radical mastectomy six weeks after her radiotherapy and a Thiersch graft with a 100% take, was shown. This illustrated the healthy state of the tumour bed and that natural repair and resistance were unimpaired. 6 out of 15 such patients are alive and free of disease at the end of five years, which though encouraging, is of no statistical value.

## Histology

This is available for all living patients. 8 survivals in one group and 6 in the other have been excluded, as histology was not available. Analysis of the type of surgery performed in combination with irradiation showed that 79% in the short course and 71% in the long course had some form of surgery and half those operated on in the short course had a simple mastectomy only, while just under a quarter in the long course had a simple mastectomy with removal of involved lymph nodes. Radical mastectomies were performed on the remainder. 21% in the short course and 29% in the long had no surgery.

Table I shows the overall survival in each group and at each stage. The improvement in results in the long course is suggestive but not statistically significant. It would appear more beneficial to the more advanced cases where surgery alone achieves so much less.

From the patient's point of view the best result is not just survival, but to undergo the initial treatment and to remain free of symptoms and signs, therefore not requiring any

further therapy. Those in the column labelled "recurrence free" satisfy these criteria. No patient received prophylactic ovarian ablation.

TABLE I.—THE FIVE-YEAR SURVIVAL AND RECURRENCE-FREE RATES

| Stage | Short course: No. of patients | Short course: % alive five years | Short course: % free of recurrence | Long course: No. of patients | Long course: % alive five years | Long course: % free of recurrence |
|---|---|---|---|---|---|---|
| I .. | 46 | 57 | 55 | 25 | 60 | 60 |
| II .. | 41 | 37 | 32 | 36 | 44 | 39 |
| III .. | 27 | 19 | 11 | 29 | 38 | 38 |
| IV .. | 48 | 4 | 0 | 68 | 19 | 14 |
| All .. | 162 | 30% | 25% | 158 | 35% | 32% |

The five-year recurrence-free rate in the long course is very close to the survival rate. McWhirter is quoted (Smithers *et al.*, 1952) as having 42·9% alive and only 31·7% recurrence free.

The three-year recurrence-free rates were compared with five-year survivals and found to give 4–8% too optimistic an estimate, though this shorter term criterion might be useful in comparative studies.

TABLE II.—SHOWS THE LOCAL RECURRENCE RATES IN THE TREATED AREA IN STAGES I–III IN THE SHORT AND LONG COURSES OF RADIOTHERAPY

| Stage | Short course: % local recurrence | Long course: % local recurrence |
|---|---|---|
| I .. .. .. | 17% | 8% |
| II .. .. .. | 22% | 17% |
| III .. .. .. | 45% | 14% |
| Total | 25% of 114 | 13% of 90 |

Table II shows the recurrence rates in the treated area: skin, axillary, supraclavicular and parasternal sites are all included. Haagensen with very strict criteria of operability gives 12·5% in the axilla and chest wall only. White (1946) at the Roosevelt Hospital gives 22·6%. Baclesse and Tailhefer (Ducuing *et al.*, 1948) quote 2% for a very strictly defined Stage I, 6% for Stage II and 30% for Stage III with surgery alone. Irradiation only succeeded in improving the Stage III rate to 12%, though their Stage III unlike the Manchester one included those with involved nodes above the clavicle.

Finally I should like to offer some evidence that treatment is worth while and that the repetition of the 39-month average survival deserves less publicity than it has received.

Statistics must be used with discretion and freak occurrences must not bias them unduly. Likewise the length of history is too unreliable to be included. None of the untreated tumours was confirmed histologically when first seen.

TABLE III.—SHOWS THE MEDIAN SURVIVAL TIME BY GROUP AND STAGE
(No. of patients in brackets)

| Stage | Short course | Long course |
|---|---|---|
| I | >5 years (48) | >5 years (25) |
| II | 4 years (44) | 4·5 years (36) |
| III | 2 years (29) | 3·5 years (29) |
| IV | 1·4 years (53) | 1·7 years (99) |

Table III shows the half-life of each group of patients by stage of the disease. It is the median survival time or the time taken for 50% to die. From figures quoted by Daland (1927) on 100 consecutive cases 1·4–1·65 years may be quoted for comparison. The median survival for all cases is two and a half and three years respectively.

To summarize:

The ten-week course gives a more flexible method of treatment and may be used either before or after operation.

It produces a significantly lower local recurrence rate.

The five-year survival rates especially the recurrence-free rates are equal to the best published, when the omission of the bulk of Stage I cases is taken into account.

The local recurrence rate, the most precise measure of the effectiveness of radiotherapy, is markedly diminished by extending treatment to a high dose over ten weeks.

Treatment undoubtedly affects the course of the disease.

No patient in the untreated series was symptom- and sign-free, nearly one-third of those treated had this additional comfort and some hope at least was given to all.

*Acknowledgement.*—I would like to thank the surgeons in the group, especially

Mr. Bernard Williams and Mr. John Younghusband, for their close collaboration, without which this work would not have been possible.

REFERENCES

DALAND, E. M. (1927) *Surg. Gynec. Obstet.*, **44**, 264.
DUCUING, J., TAILHEFER, A., and BACLESSE, F. (1948) *P.V. Ass. franç. Chir.*, **51**, 1.
HAAGENSEN, C. D., and STOUT, A. P. (1951) *Ann. Surg.*, **134**, 151.
SMITHERS, D. W., RIGBY-JONES, P., GALTON, D. A. G., and PAYNE, P. M. (1952) *Brit. J. Radiol.*, suppl. No. 4, p. 66.
WHITE, W. C. (1946) *Surgery*, **19**, 149.

## The Value of Histology in the Prognosis and Classification of Breast Cancer

By H. J. G. BLOOM, M.D., M.R.C.P., F.F.R.
*London*

THE clinical progress of patients with carcinoma of the breast is so variable that perhaps we should be nearer to solving the problems of treatment if we regarded this disease as being caused, not by a single tumour type, but by a group of tumours with a broad spectrum of malignancy.

The outcome of treatment may be quite different even in patients of similar age, with the same duration of symptoms and with tumours of comparable clinical extent. In addition, identical lines of treatment may give variable results, and equally good results have been obtained by radical and more conservative procedures. It is facts such as these which make the management of operable breast cancer still a subject for debate, even though ninety years have elapsed since the first type of radical mastectomy was introduced by Moore of the Middlesex Hospital (Moore, 1867).

The chief purpose of this paper is to present evidence in support of the view that differing opinions regarding treatment have arisen largely from comparing results in groups of patients not strictly comparable, and to propose a more accurate classification of the disease.

The generally accepted classification of carcinoma of the breast provides a guide only to the obvious extent of the tumour. Early death in what appear to have been favourable cases must indicate the presence of highly malignant occult metastases at the time of treatment. Delayed death in advanced cases points to metastases of low-grade malignancy. The failure to detect subclinical metastases in so-called early cases and the inability to assess the speed with which such metastases are likely to develop, are responsible for many of the discrepancies which result from staging.

Can staging be made more accurate? The fallacy of trying to decide whether the axillary lymph nodes are involved or not by clinical examination is well known. About 40% of non-palpable nodes show histological invasion, and some 20% of palpable nodes are histologically free (Harnett, 1948; Haagensen, 1956). The routine microscopic examination of lymph glands from the axilla and also the internal mammary chain (Handley and Thackray, 1954) will, no doubt, add to the value of staging, but even this procedure is open to considerable error. Thus, Saphir and Amromin (1948) find that serial sections demonstrate axillary involvement in one-third of cases previously reported as being histologically free.

Staging, in its present form, will always be of limited value in the study of breast cancer, and it is difficult to see how further improvements in this type of classification can be brought about. Hence, a method of determining the potential malignancy of the tumour may provide a more accurate guide to prognosis than measuring the clinical extent of the growth. By "potential malignancy" is meant the proneness of the tumour to metastasize early or late.

Some indication of the degree of malignancy of breast cancer can be obtained from the histological architecture of the tumour, and it is convenient to express this in terms of a simple numerical grading system. This provides a guide to the likelihood of involvement of those structures not adequately considered by staging, and also to the speed with which metastases may develop, give rise to symptoms and finally cause death (Bloom and Richardson, 1957). Grading of carcinoma of the breast was introduced into this country by Patey and Scarff (1928) who followed the principles formulated by Greenough (1925) in the United States. The method, which is simple to apply and has proved an effective guide to prognosis, is based on three histological criteria, namely, degree of tubule formation, regularity of nuclei, and frequency of hyperchromatic and mitotic figures (Bloom, 1950). Taking the histological picture as a whole each tumour is then classified as being of low, intermediate or high malignancy, grades I, II and III respectively (Figs. 1–3). Needless to say, these three types of tumour are not entities, but merely represent arbitrary subdivisions of a continuous malignant scale. Details and problems of this technique of grading have been described fully elsewhere (Bloom and Richardson, 1957).

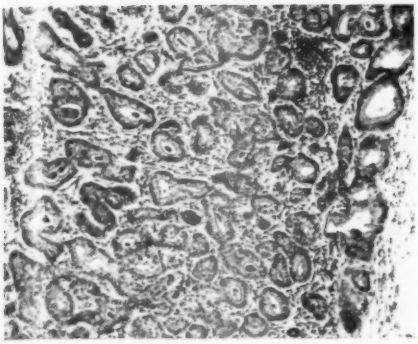


FIG. 1.

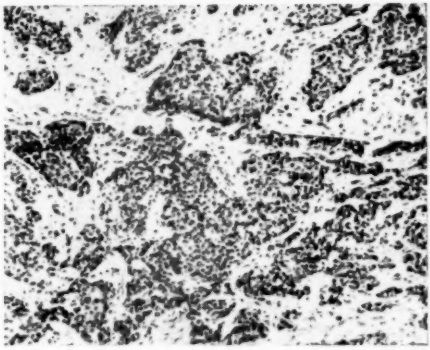


FIG. 2.

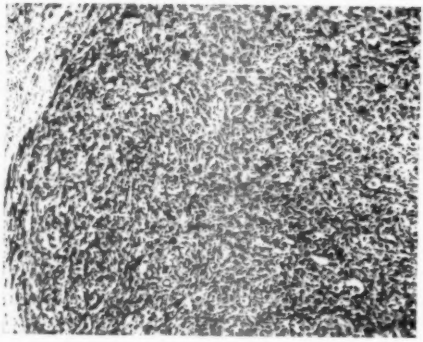


FIG. 3.

FIG. 1.—Highly-differentiated grade I tumour showing well-marked tubule formation, uniform nuclei, and very infrequent mitoses. ×55.

FIG. 2.—Grade II tumour with only very occasional tubules, a moderate degree of nuclear irregularity, and a fair number of hyperchromatic and mitotic figures. ×70.

FIG. 3.—Gross disorder in this grade III carcinoma. No attempt at tubule formation, marked irregularity of nuclei, and numerous hyperchromatic and mitotic figures. ×54.

For further examples *see* Bloom and Richardson (1957).

## MATERIAL

The histological sections of 1,409 female breast cancers, seen at the Middlesex Hospital between 1936 and 1949, have been graded on the lines just described. Approximately one-third of the cases were graded by myself, and the remaining two-thirds in association with Mr. W. W. Richardson. Rather less than half the cases (45%) were found to be of intermediate malignancy; the remaining cases were divided approximately equally between the high and low grades, 26% and 29% respectively.

Only when grading had been completed were the clinical notes examined. It must be pointed out that the figures which follow are based on a selected series of cases because of the necessity of having to have histological material for grading. Although the method of treatment was not uniform, the majority of patients (84%) had a radical or modified radical mastectomy with or without ancillary irradiation.

## GRADE AND PROGNOSIS

The survival rate at five, ten and fifteen years after treatment was determined for each of the three grades of malignancy, and the results are shown in Table I and Fig. 4. A correlation

TABLE I.—HISTOLOGICAL GRADE AND PROGNOSIS

| | 5-year results | | 10-year results | | 15-year results | |
|---|---|---|---|---|---|---|
| Grade | Cases 1936–49 | Survivals | Cases 1936–45 | Survivals | Cases 1936–40 | Survivals |
| I .. | 362 | 75% | 215 | 53% | 96 | 31% |
| II .. | 640 | 47% | 349 | 27% | 162 | 18% |
| III .. | 407 | 32% | 250 | 19% | 101 | 10% |
| Total | 1,409 | 50% | 814 | 31% | 359 | 19% |

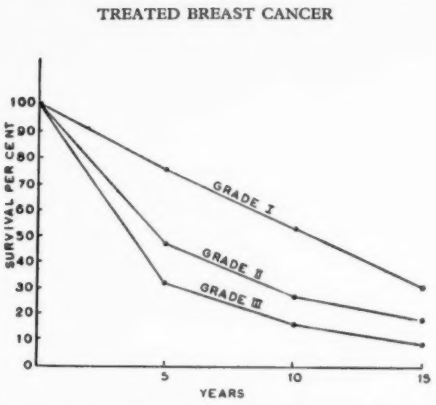



FIG. 4.—Grade and prognosis (5, 10 and 15-year survival rates).

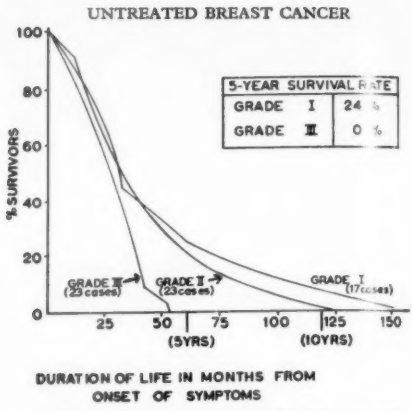



FIG. 5.—Grade and prognosis 63 cases with histology observed at the Middlesex Hospital.

Figs. 4 and 5 are taken from Bloom and Richardson (1957) by kind permission of the Editor of the *British Journal of Cancer*.

has been found between histological structure and prognosis, the survival rate for patients with grade I tumours being two to three times greater than that for grade III cases. The prognosis for grade I cases at fifteen years is comparable with that for grade III cases at five years. It is evident that the survival rate for grade I cases, so promising at five years, eventually proves disappointing in that a steady decline continues throughout the fifteen years of observation. On the other hand, the grade III survival curve shows that most of the deaths from this type of tumour occur within the first five years. Thus, an interval of five years is of considerably less value in determining the results of treatment for women with grade I tumours than with grade III lesions.

### GRADING OF UNTREATED BREAST CANCER

Further support for the concept of three grades of malignancy comes from a study of patients with untreated breast cancer at present being carried out at the Middlesex Hospital. The patients, who were seen between 1805 and 1920, included 63 from whom biopsies had been taken. These have been classified according to grade, and the survival rate, based on the duration of life from *onset of symptoms*, is shown for the three types of tumour in Fig. 5. A clear distinction is again demonstrated between grade I and grade III tumours.

### GRADING OR STAGING AS A CLASSIFICATION FOR BREAST CANCER

Although histological grading provides a useful guide to prognosis it is of no greater value than clinical staging. Both systems of grouping give comparable results (Table II). Adequate information for assessing the stage was not available in 18 cases. The

TABLE II.—COMPARISON OF STAGING AND GRADING FOR PROGNOSIS

| | Five-year survivals | | |
|---|---|---|---|
| Stage | Cases | Grade | Cases |
| 1 | 75% | I | 75% |
| 2 | 43% | II | 47% |
| 3 | 34% | III | 32% |
| 4 | 8% | | |
| Total (1,391) | 50% | Total (1,391) | 50% |

Manchester system of staging (Paterson, 1948) has been used here, but for accuracy, where possible, axillary node involvement was based upon histological examination. Even this method gives practically no more information regarding prognosis than study of a section of the patient's tumour.

### GRADING AND STAGING COMBINED FOR CLASSIFICATION OF BREAST CANCER

Earlier reports have indicated that a more accurate guide to prognosis can be obtained by linking clinical stage and histological grade than by either factor alone (Bloom, 1950*a*, 195 ). This combined classification takes into account both the apparent extent of the tumour when

the patient is first seen and its potential malignancy. The latter provides some indication as to the likely existence and malignancy of occult metastases. The effect of grouping the present series of cases according to stage and grade for prognosis at five, ten and fifteen years after treatment is shown in Table III.

TABLE III.—STAGE, GRADE AND PROGNOSIS

| Stage | Grade | Five-year results Cases 1936–49 | Five-year results Survivals | Ten-year results Cases 1936–45 | Ten-year results Survivals | Fifteen-year results Cases 1936–40 | Fifteen-year results Survivals |
|---|---|---|---|---|---|---|---|
| 1 | I | 162 | 86% | 98 | 55% | 45 | 40% |
| | II | 212 | 70% | 109 | 49% | 50 | 34% |
| | III | 93 | 70% | 58 | 48% | 22 | 27% |
| 2 | I | 120 | 71% | 66 | 58% | 21 | 19% |
| | II | 247 | 42% | 131 | 22% | 50 | 16% |
| | III | 181 | 25% | 103 | 12% | 38 | 10% |
| 3 | I | 63 | 67% | 45 | 42% | 28 | 28% |
| | II | 130 | 30% | 76 | 13% | 41 | 7% |
| | III | 97 | 19% | 64 | 9% | 26 | 0% |
| 4 | I | 11 | 36% | 2 | 50% | — | — |
| | II | 42 | 5% | 28 | 4% | 19 | 5% |
| | III | 33 | 3% | 24 | 4% | 15 | 0% |
| | Total | 1,391 | 50% | 804 | 31% | 355 | 17% |

The number of patients alive at five years ranges from as high as 86% for stage 1, grade I cases, down to a mere 3% for those in stage 4, grade III (Table III). Note the variation in prognosis within each stage where there is, generally speaking, a marked deterioration in survival rate with rise in histological malignancy. The high survival rate of the grade I cases in every stage of the disease is striking. Thus the outlook for grade I cases in stage 3 is more favourable than that for the majority of patients in stage 2 (i.e. those in grades II and III), and almost as good as that for many in stage 1 (i.e. again those in grades II and III). The prognosis for grade III cases in stage 1 appears to be relatively good, indicating that at least some highly malignant tumours are probably still localised to the breast region at the time of treatment. However, these cases constitute only 7% of the total series and 20% of stage 1 patients.

The ten-year follow-up of some 800 patients reveals a comparable pattern of results with 55% survivals at one end of the scale and 4% at the other end. The same pattern is again seen in 355 patients who have been followed for fifteen years and the corresponding figures are 40% and 0%.

This clinico-pathological classification reveals that hope need not be abandoned even for patients with stage 3 breast cancer, provided that their tumours are of low-grade malignancy. Furthermore, it seeks to explain some of the disasters among stage 1 patients and many of the disappointments in stage 2, the failures in either stage being largely due to the presence of the more malignant grade II and grade III tumours.

## FACTORS WHICH MAY INFLUENCE THE GRADE OF MALIGNANCY IN BREAST CANCER

Nothing is known of possible hereditary, racial or geographical factors upon the incidence of the three grades of malignancy. The patient's age, so often claimed to be of importance in prognosis, has been found without influence on tumour type (Bloom, 1950*b*). At the present time the only known factor capable of influencing the grade of breast cancer is child-bearing.

Carcinoma of the breast, when associated with pregnancy or lactation, carries a particularly bad prognosis (White, 1955). In my series of 90 patients (Bloom, 1955) the majority of the tumours (64%) were of high malignancy (grade III), whereas only 4% were classified as grade I. This is in marked contrast to the general series reported here where there is approximately an equal incidence of low and high grade tumours, 26% and 29% respectively.

## CONCLUSIONS

The relative value of different lines of treatment in breast cancer appears impossible to assess accurately, whilst patients with tumours of widely differing malignancy continue to be grouped together for comparative studies. Such heterogenous groups of cases are produced by clinical staging and the widespread use of this system may be responsible for at least some of the confusion concerning treatment. The position is unlikely to be clarified

until a more accurate classification of the disease is employed. The combination of clinical staging and histological grading is offered as a step in this direction.

I would like to express my gratitude to Professor B. W. Windeyer and Professor R. W. Scarff for facilities to work on the problems associated with breast cancer, and to the many surgeons whose cases have been studied.

REFERENCES

BLOOM, H. J. G. (1950*a*) *Brit. J. Cancer*, **4**, 259.
—— (1950*b*) *Brit. J. Cancer*, **4**, 347.
—— (1955) *Rep. Brit. Emp. Cancer Campgn*, **33**, 30.
—— (1956) *Brit. J. Radiol.*, **29**, 488.
——, and RICHARDSON, W. W. (1957) *Brit. J. Cancer*, **11**, 359.
GREENOUGH, R. B. (1925) *J. Cancer Res.*, **9**, 453.
HAAGENSEN, C. D. (1956) Diseases of the Breast. Philadelphia; p. 92.
HANDLEY, R. S., and THACKRAY, A. C. (1954) *Brit. med. J.*, i, 61.
HARNETT, W. L. (1948) *Brit. J. Cancer*, **2**, 212.
MOORE, C. H. (1867) *Med.-chir. Trans.*, **50**, 245.
PATERSON, R. (1948) Treatment of Malignant Disease by Radium and X-rays. London; p. 309.
PATEY, D. H., and SCARFF, R. W. (1928) *Lancet*, i, 801.
SAPHIR, O., and AMROMIN, G. D. (1948) *Cancer*, **1**, 238.
WHITE, T. T. (1955) *Amer. J. Obstet. Gynec.*, **69**, 1277.

[*November* 15, 1957]

## Vision, Photography and Electronics in Radiology [*Précis*]

By G. E. DONOVAN, M.D., M.Sc., D.P.H.
*Swansea*

and E. STAFFORD, B.Sc., B.A.
*Manchester*

THE study of radiographs involves the light-adapted eye which perceives contrast differences best in the range 10 millilamberts to 10 lamberts. A modern illuminator approximates to 450 millilamberts. Adaptation to light is rapid and is nearly complete in the first half-minute. In contradistinction dark adaptation takes place more slowly and continues for about twenty-four hours when a brightness value of 0·000001 millilambert may be perceived. Increase of sensitivity rises steeply for the first twenty minutes.

Dark-adapted vision is mainly by rods which means that there is a relative central scotoma. This is important in fluoroscopy.

Since rods are poorly sensitive to red light the wearing of red goggles for dark adaptation has a physiological rationale.

Dark adaptation becomes less effective with age, the light perception being about twice as good at 20 years of age as at 40, after a given period of dark adaptation.

The visual acuity (i.e. resolution of fine detail) falls with low intensity of light. Where in a good light points 0·0006 in. apart can be resolved into two, this may increase to 0·04 in. under conditions of fluoroscopy. Similarly intensity discrimination which may allow a 1% difference to be perceived in daylight may be as low as 40% in screening a thick subject.

Dr. Donovan dealt with factors which facilitate *good interpretation* of the radiograph which involves an interplay of experience and intelligence on the part of the observer with an optimal presentation of the data in the film.

Factors related to *definition and contrast* in the negative were discussed.

Some aspects of *density differentiation* and the possible application of colour to the recording of different tissue densities were mentioned.

*Image intensification.* Various devices either now in use or potential methods of intensification were briefly discussed with the advantages and defects of the present systems.

Experiments are now going forward with *electro-luminescence* as a source of energy magnification which involves only a thin plate comparable to the present X-ray screen. This has interesting possibilities and may be the eventual answer.

The paper ended with a reference to the influence of *automation* in future development.

# Section of the History of Medicine

President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., C.B., M.A., D.M., F.R.C.P.

[*November* 6, 1957]

## Thudichum and the Medical Chemistry of the 1860s to 1880s

By HENRY MCILWAIN, D.SC.

*Department of Biochemistry, Institute of Psychiatry, Maudsley Hospital, London*

JOHANN LUDWIG WILHELM THUDICHUM (1828–1901) has been claimed as the father of neurochemistry; in this sphere I see him as a notable successor to many previous workers (McIlwain, 1958), and here I wish first to indicate his position in the medical chemistry of the mid-nineteenth century.

Sudhoff (1932; Table I) describes how, when Thudichum was about 18 years old, his

TABLE I.—J. L. W. THUDICHUM 1828–1901: SYNOPSIS OF CAREER AND PUBLICATIONS

| | |
|---|---|
| 1847 | Meets Liebig; enters the University of Giessen. |
| 1851 | M.D.Giessen. Thesis: "Fractures of the upper end of the humerus". |
| 1854 | M.R.C.S.London. |
| 1856 | Physician, St. Pancras Dispensary. |
| 1858–63 | Lecturer in Chemistry, Grosvenor Place School of Medicine. |
| 1858 | A Treatise on the Pathology of the Urine (Churchill, London: 2nd edit., 1877). |
| 1863 | A Treatise on Gall-stones (Churchill, London). |
| 1865 | Lecturer in Pathological Chemistry, St. Thomas' Hospital. |
| 1866–82 | Research for the Medical Officer to the Privy Council and later to the Local Government Board, appearing in the Public Health Reports. |
| 1872 | A Manual of Chemical Physiology including its points of contact with pathology (Longmans, Green, Reader & Dyer, London). |
| 1872 | A Treatise on the Origin, Nature and Varieties of Wine (with A. Dupré. Macmillan, London). |
| 1879–81 | *Annals of Chemical Medicine, including the application of chemistry to physiology, pathology, therapeutics, pharmacy, toxicology and hygiene* (Longmans, Green, London). |
| 1884 | A Treatise on the Chemical Constitution of the Brain (Baillière, Tindall & Cox, London). |
| 1886 | Anatomischen und Klinischen Chemie (Berlin). |
| 1894 | A Treatise on Wines. Their Origin, Nature and Varieties, with Practical Directions for Viticulture and Vinification (Bell, London). |
| 1895 | The Spirit of Cookery (Baillière, Tindall & Cox, London). |
| 1901 | Die chemische Konstitution des Gehirns des Menschen und der Tiere (Pietzcker, Tübingen). |

father consulted Justus Liebig about the analysis of mineral waters from a newly discovered spring. The son Ludwig met the great chemist and was oriented towards chemistry before he entered the University of Giessen as a medical student. Here he obtained his doctorate in 1851 with a thesis on an anatomical subject; but even before this he had worked with Liebig in the inspiring environment of his busy and pioneering laboratory; he regarded himself throughout his life as Liebig's pupil. His position in Giessen (in Hesse) was, however, made difficult because a few years earlier during war with Denmark he had served voluntarily in a medical capacity in the army of Schleswig-Holstein. In this situation he left for London where a family he already knew well had recently established themselves: in particular Augustus Dupré who had become Lecturer in Chemistry at Westminster Hospital Medical School, and his sister Charlotte who married Thudichum soon after he arrived in London. Thudichum also promptly obtained his M.R.C.S.; then an appointment as physician, and he was in medical practice throughout his life, especially as an otologist and rhinologist. He contributed papers in this specialty, and devised a "Thudichum nasal speculum" but these activities form a small part only of his scientific output.

Thudichum's chemical interests first found official expression in England in 1858 through his appointment as lecturer in Chemistry at the Grosvenor Place School of Medicine. Later he was lecturer in pathological chemistry at St. Thomas's Hospital, and director there of the newly founded pathological and chemical laboratory (Obituary, 1901). He was thus concerned just a hundred years ago, with teaching to medical students the rapidly expanding subject of medical chemistry. In 1858 he published his first book, on the analysis of urine.

Teaching and writing in medical chemistry underwent a considerable change in the second quarter of the nineteenth century: during, that is, the period between Thudichum's birth and his beginning as a lecturer. At the beginning of the 1800s, chemistry was being taught to students of medicine in some if not all the medical schools in Britain, but taught in much

the same fashion as chemistry would be taught to students in science. Paris's (1825) "Medical Chemistry" is an example. Though addressed very specifically to students of medicine, the book has throughout an entirely chemical framework and a large part concerns purely inorganic chemistry. Much of the material taught was in fact that of our present school chemistry (and physics) which of course is still taught with a purely chemical logic, as a means of introducing chemical principles and discovery, whether or not the students concerned are later to be trained in medicine or another subject.

It can thus be seen that the type of medical chemistry on which Thudichum began to publish in 1858 was a relatively new subject: representing a stage in the formation of what became the typical physiological chemistry as it was taught in medical schools in the decades around 1900. I would like therefore to look more closely at the environment in which this first book appeared.

Firstly, Thudichum's was one of several books on the same general subject published in the middle of the last century. In the decade 1854–1865, the Surgeon-General's Catalogues and other sources indicate the books of Table II, concerning analysis of urine, to have appeared together with about an equal number of publications in thesis or analogous form.

TABLE II.—THUDICHUM'S FIRST BOOK WITH COGNATE PUBLICATIONS

Neubauer, C. (1854) Anleitung zur qualitativen und quantitativen Analyse des Harns. Wiesbaden.

Hellerman, J. F. (1855) Pathological Chemistry of the Urine. Trans. L. Dahl. Dublin.

Beale, L. S. (1856) Tables for the chemical and microscopical examination of urine in health and disease. London.

Thudichum, J. L. W. (1858) A Treatise on the Pathology of the Urine, including a complete guide to its analysis. London.

Parkes, E. A. (1860) The composition of the Urine in health and disease and under the action of remedies. London.

Beale, L. S. (1861) On Urine, Urinary deposits and calculi, their microscopic and chemical examination. London.

Hassall, A. H. (1863) The Urine in health and disease, being an exposition of the composition of the urine and of the pathology and treatment of urinary and renal disorders. London (1st Edition, 1859).

Neubauer, C. and Vogel, J. (1863) A Guide to the qualitative and quantitative Analysis of the Urine, designed especially for the use of medical men. Transl. Markham, New Sydenham Society, London.

All these were practical handbooks dealing with this relatively narrow subject, and before and after this especially prolific decade such publications were less frequent. Thudichum's deals with urinary constituents and does not, for instance, begin with a general statement of kidney function or the role of the urine or its relationship to the blood. Although these subjects are touched on in dealing with individual constituents, they form a very small and disconnected part of the whole, as also do the book's pathological aspects.

Now both before and since the 1850s, many more general books on physiological chemistry appeared. An example, very relevant to Thudichum in London, was the "Practical Handbook of Medical Chemistry" of J. E. Bowman of King's College, London, which went through three editions between 1850 and 1855; designed as a "small manual giving instruction for the examination and analysis of urine, blood, and a few other of the more important animal products, healthy and morbid; and comprising also, directions for the detection of poisons in inorganic mixtures and in the tissues". Nearly half of this book deals with urine, but from a practical point of view it is very different from its successors of Table II. The methods both for urine and blood in Bowman's book are very cumbersome, depending largely on actually separating and weighing constituents, including urea. An analysis begins with 10 or 12 oz. of blood.

By contrast, the manuals of what we may call the new analytical specialists of Table II were excellently businesslike. Several volumetric methods are described, which are much more speedy than gravimetric ones. Thudichum with the other authors was, in effect, presenting some fifty years' research by many investigators on the application of analytical methods to bodily materials, with the object of aiding diagnosis and treatment. To appreciate this, it may be noted, firstly, that Fourcroy at the end of the eighteenth century began the section on the animal kingdom in his "Elements of Natural History and Chemistry" (1790) by saying how the analysis of animal substances in general was in a much more imperfect state than other branches of the science. With respect to urine, he writes "The state of the stomach, and particular humours . . . cause infinite diversity of changes in this fluid, to ascertain and estimate which, a long series of experiments would be requisite, which have, as yet, only been pointed out as necessary."

Secondly, if we look at the achievements of the years before the publications of Table I, we find they had been unusually prolific, and feature many subjects and names still familiar in physiological chemistry. Thus, though the volume and sweetness of the urine had long

been prominent in diabetes mellitus, Trommer first developed a chemical test for the sugar, depending on oxidation by alkaline copper salts, in 1841; Fehling's quantitative method came only in 1850. The peculiar smell of the breath in this condition was definitely ascribed to acetone, and a test for this in urine devised by Petters in 1857. Albumin was noted as an abnormal constituent of urine in 1812, and the biuret test for urinary albumin described in 1833; Millon's reaction for proteins dates from 1849. In 1848 Bence-Jones reported the urinary proteins associated with a particular softening of the bones. Pettenkofer's test for bile-salts in urine came in 1844.

Chemical analysis was thus making real contributions to the understanding and diagnosis of disease and this new, applied medical chemistry largely concerned the urine. The nature of the urine makes it understandable that it, rather than other body fluids or tissues, should first have received the large attention indicated by Table II. It contains relatively little of the proteins, mucilages and formed elements which make blood, milk or flesh more difficult to examine. Simple substances such as urea and inorganic salts form a large part of its solid matter. Apart from the examination of the urine to aid the diagnosis or treatment of disease, two other stimuli to its study can be recognized in the first half of the 1800s, perhaps especially in Thudichum's work. First, the examination represented part of the growing organic chemistry of the times: a wide variety of materials associated with living organisms were being ransacked for their chemical constituents, which were being analysed and the analyses collated to yield chemical patterns. These had not in Thudichum's book of 1858 become the structural or even empirical formulæ of to-day: the subject was in his time still in course of development. Secondly, the analyses of foodstuffs, tissues and excreta were giving real enlightenment in physiology and here Liebig, with the new concept of metabolism expressed chemically, was a pioneer.

The books of Table II, which reflect this first major application of chemical analysis in medicine, appear from this distance to represent the type of technical elaboration through which a new specialty frequently passes before taking its place as a valuable but limited tool, available with the minimum of trouble to those who are to apply it to practical problems. Of all the books, Thudichum's probably represents the greatest chemical elaboration. Its organisation is purely chemical, with some 50 chapters, mostly of a few pages and dealing with an individual urinary constituent or group of constituents. These chapters are usually excellent, brief, well-documented monographs on the constituents concerned, giving, for instance, their chemical nature, discovery, chemical and physical properties, isolation or determination. But often less than half of the account deals with the substance as it occurs in urine. Thus there are described the crystallography of sodium chloride, the solubility of creatine, the chemical synthesis of urea: information for which one would now consult texts on inorganic chemistry, physics, or organic chemistry. On the other hand, it is to be emphasized that knowing as much as possible about the chemistry of all urinary constituents did give the basis for the discovery of new constituents and for the development of new analytical methods. Thus Thudichum's book might have been a manual for those who were hoping to make new chemical discovery regarding the urine in pathological conditions, though actual achievement in this respect formed only a small part of it.

Thudichum's next major work concerned a second subject which was typical of the growing chemical pathology of the time: "A Treatise on Gall Stones: their Chemistry, Pathology and Treatment" (1863). It has fewer compeers than his book on urine; in his Introduction Thudichum states his aim of giving an account of the chemistry of gall stones comparable to Morgagni's description of their physical nature. The book displays Thudichum not only as a chemist, but also as a microscopist, for he found casts of bile ducts in the centre of the stones; and as a theorist, for he writes fifty pages on previous chemical work, and in a final section nearly as long he debates both chemical and physical factors in the formation of the stones. Here he emphasizes the presence of the bile acids as binding materials and concludes the stones to be formed "by a decomposition of the bile akin to putrefaction". But this is too early a date to expect adequate experiments in such matters; Thudichum's experiments on the changes occurring on standing bile for some years are not impressive. More noteworthy are his isolation of bile pigments from the stones, and his contribution to their chemical classification. Also, two similarities between the investigation of urine and gall stones are worth bearing in mind in relation to Thudichum's subsequent work. First, presumably in his search for chemically tractable materials, Thudichum has chosen to study a very limited part of the body. Second, he is working within a limited range of chemical study, being primarily concerned with the isolation and analysis of chemical substances.

### Thudichum's Practical Work and Work on the Brain

Thudichum's book on the urine, and also his later "Manual of Chemical Physiology" (1872) are eminently practical books: they give excellent manipulative instructions and much quantitative data needed by a laboratory worker. I would now like to indicate the circum-

stances in which the greater part of Thudichum's laboratory work was carried out, for they were unusual in his day and would also be so in ours. Thudichum had received his training under Liebig who from the 1830s was a pioneer in teaching by laboratory investigations, and as such attracted workers from all over Europe and beyond. It is understandable that the facilities which Thudichum first obtained with his hospital or medical school appointment fell far below this standard, though in his second appointment, at St. Thomas's, he was director of a new pathological and chemical laboratory and some work published in 1869 is described as being performed there. The bulk of his work, however, both before and after that time, was carried out in a laboratory which he had established in his private house. More remarkable, Thudichum was given support or expenses from Government sources. This took place through his carrying out investigations for the Medical Officer to the Privy Council initially into the chemical pathology of infectious diseases. Such payment for work done was perhaps not fundamentally different from payments to medical consultants or to consultant analysts. With Thudichum, however, the arrangement was unusual in being primarily for research, in what became quite a broad and abstruse subject, and which lasted for some years. The Medical Officer concerned, whose attention had been attracted by Thudichum's work and who charged him with these investigations (Obituary, 1901; Sudhoff, 1932) was the notable Sir John Simon. Simon was initially responsible to the Privy Council and so in a relationship similar to that of the Medical Research Council established some forty or fifty years later. In the latter part of Thudichum's work Sir John Simon was responsible to the Local Government Board.

At first Thudichum carried out analyses on material on which Simon made other pathological studies but shortly Thudichum's work appears to have become entirely independent. Quite early he had qualified assistants. Throughout, his work appeared in the Annual Report of the Medical Officer, introduced by Simon but often carrying long technical supplements by Thudichum in which he gave theoretical and practical details of his work. Thudichum more than anyone else appears to have availed himself for sixteen years of this opportunity to make the Reports a medium for publishing in what we would now regard as the basic medical sciences. Moreover the Reports at least in one quarter almost became known as a periodical in biological chemistry: Chittenden (1930) in his history of physiological chemistry in the United States describes them as eagerly awaited there. On the other hand, this mode of publication probably contributed to some of Thudichum's work being overlooked. Much of it, however, was published a second time either in ordinary journals or, after a lapse of some years, in book form.

Thudichum's studies for the Medical Officer were clearly planned as a fundamental attack on a major medical problem of the time. He begins his first report: "The object of these researches, proposed to me on the 7th August 1866 by the Medical Officer of the Privy Council were as follows: 'By investigation of choleraic discharges, and of the diseased body after death, and by such auxiliary observations of the sick as may be needful, to ascertain *what successive chemical changes are undergone by the body in the progress of cholera, and what relation subsists between those changes and the symptoms presented by the patient during life*'." Thudichum's previous work clearly fitted him for such studies, and his report on this occasion covers some 50 pages, giving examinations of urine, blood, bile, stools, muscle and liver from many cases; describing new methods in detail including the use of the spectroscope in which Thudichum did pioneer work.[1]

In 1868 and in subsequent years the direct study of cholera has less prominence and Thudichum's section in the Reports is headed *Researches intended to promote an improved chemical identification of diseases*. Thudichum in 1868 argues this subject in general terms, not confining himself to his own researches but writing rather in textbook or monograph style, concluding, for example, that "Ultimate pathology cannot, I think, be cellular, as was claimed by Virchow". He notes that not enough is known of the constituents of bodily organs to make likely the detection of chemical change in pathological conditions. Here he instances the relatively well-investigated extract of muscle (Thudichum had written on Liebig's meat extract), pointing out that in spite of much investigation some five-sixths of its constituent material was still unidentified. This is the light in which we are to see Thudichum's detailed chemical studies: and very detailed they were. For example, the

[1]An interesting sidelight on Thudichum's spectral analysis is described by Duncum (1947). During the 1860s Thudichum demonstrated its abilities to the Medical Society of London and used cylinders of compressed oxygen and hydrogen for his source of light. This was observed by Charles James Fox, who was seeking a way to make nitrous oxide manageable for anæsthesia. Fox persuaded the firm of Coxeter to compress nitrous oxide for anæsthetic use and from 1870 was using it widely in the Dental Hospital, London. At this point we have a reminder of Thudichum as a patriot and humanitarian, for during the Franco-Prussian War he is described as making an urgent newspaper appeal for the supply of nitrous oxide for military surgery. Over £180 was subscribed to a Nitrous Oxide Fund and Coxeter supplied over 5,000 gallons of the gas for this purpose, Thudichum going to the theatre of war to see it applied.

examined urinary pigments, and the pigments of bile and gall stones; reported on "a new series of yellow compounds contained in animals and plants" which Rosenheim (1930) later took as pioneering work in carotenoids. He studied proteins and amino acids, characterizing a new amino acid "glycoleucine", or norleucine.

Moreover, it was in this spirit and background that Thudichum carried out his major original work which was on chemical constituents of the brain. His first large report of his own investigations in this subject came in 1874 and his book, "The Chemical Constitution of the Brain," in 1884. It is clear from both these sources and also from John Simon's own Reports, that Thudichum was carrying out very extensive and purely chemical studies of the normal composition of the brain, usually of ox brain, in order to understand and control the deliria and coma of cholera, typhoid, and other infections. To appraise this we must recall the late 1860s when Thudichum's work on cholera began. Fevers with their prominent, distressing, mental symptoms, were the major medical problem of the day. Bacteriology had not begun. Microscopic observations of the brain were still rudimentary. Presumably it seemed reasonable to others as well as to Thudichum, that chemistry which could demonstrate abnormal glucose or urea in a normal-looking urine, might also help to specify the material basis for disorder in a normal-looking brain. At any rate one can imagine it worth trying. Thudichum, however, had a rather more rigid view and even in 1884 appears to be making little attempt to consider what was the most profitable line of attack. For he was primarily a chemist and had found great chemical complexity in the brain. As he wrote after his twelve years of investigations, "unforeseen complications arose". His list of chemical substances isolated from the brain, and either partly or completely characterized, runs to some 140 (Thudichum, 1901). I have appraised elsewhere something of the great enterprise and some shortcomings of this work (McIlwain, 1955, 1958; Page, 1937). Thudichum's purifications and analyses were very painstaking, and were carried out at a time when about a gram of material was required for adequate characterization and analysis. Much of this work, therefore, may never again be done in the same way or on the same scale; and we are fortunate that some of Thudichum's specimens have been preserved. In 1930 Dr. Rosenheim of the National Institute for Medical Research visited two daughters of Thudichum and was given laboratory records, other writings of Thudichum, and also a large collection of his chemical specimens. These were exhibited to the Biochemical Society in 1930 and are now at the National Institute, Mill Hill.

In the present setting we may note that Thudichum, although knowing how much more difficult would be his new task than that of the chemical understanding of urine or gall stones, nevertheless tackled it energetically. I wish to emphasize that Thudichum still, in 1884, wrote "When the normal composition of the brain shall be known to the uttermost item, then pathology can begin its search for abnormal compounds or derangements of quantities. . . . The knowledge of the composition and the properties of neuroplasm and of its constituents will also aid us in devising modes of medical treatment. . ." Here he was doing little more than restating his programme of twelve years ago, perhaps in the hope that others would continue his work. For he was then 56 years of age, still active in medical practice, with a family of six children and with many other interests. In the report dated December 1883, George Buchanan as Medical Officer wrote "Dr. Thudichum has now completed those profound researches into the chemistry of the brain, on which he has been so long engaged for the Board. . . His researches have shown, he says, the brain to be the most diversified chemical laboratory of the animal body; all other organs being much more simple and very much less specific in their chemical constitution than the organs producing and conducting nerve power". This conveys the enthusiasm of a specialist, with a turn of phrase about nerve power which betrays ignorance of a quarter century of physiological study of the nervous system. The phrase is Thudichum's; it appears in his book of 1884.

### Chemistry in Physiology and Medicine

In 1872 appeared his "Manual of Chemical Physiology including its points of contact with Pathology". Like his book on urine, this is one of a number of books on the same general subject produced by different authors at this time. Thudichum's begins in a familiar fashion with an account of digestion; of the chemical effects of saliva, gastric and pancreatic juices. He naturally has a section on the brain, but the most distinctive part is the relatively large and detailed "analytical guide" giving excellent laboratory descriptions of experiments to display the chemistry of the component tissues and substances of the animal body. Many experiments are of a type which has persisted through the subsequent eighty years, and one may suspect it to be Thudichum's medical school experience which prompted him to write in the book's preface ". . . I think it improbable that ordinary students of medicine will go easily through the whole of its matter in the laboratory. I hope therefore that teachers of chemistry who will make use of the guide will select the reactions and analyses to be performed by each student, according to his knowledge, ability and intentions". Conceivably because of its

good practical guide as well as the date of its publication, this was the first text on physiological chemistry to be used in the United States when, in 1874, the subject began to be taught with laboratory work at Yale (Chittenden, 1930).

Of very different character are the two volumes of Thudichum's *Annals of Chemical Medicine, including the application of chemistry to physiology, pathology, therapeutics, pharmacy, toxicology and hygiene* (1879, 1881). This was intended to be an abstract or review journal in the subjects named. It thus represented a considerable enterprise, and was the nearest approach in English to Maly's *Jahresbericht über die Fortschritte der Thierchemie* which had been published since 1873. In general, Thudichum's like Maly's consisted of annoted summaries of publications from all sources. It also, however, contained much of Thudichum's own work and was nearly all written by himself. Moreover, from time to time it displays Thudichum polemically defending details of his previous work. Thus he felt, probably rightly, that his work had been slighted or distorted by certain authors including Gamgee in this country and Hoppe-Seyler in Germany; here, in the *Annals*, Thudichum forcefully gave his opinions. Less excusably, the *Annals* also occasionally displays really splenetic views of work which Thudichum was not in a good position to judge. One treated so was Kühne on his discovery of the bleaching of visual pigments by light, observations which Thudichum disparaged and mocked (*see* McIlwain, 1958). For Thudichum was a protagonist not of all types of application of chemistry in medicine, but of one particular type: the separation, purification, and analysis of compounds from natural sources.

Thudichum must have realized a growing lack of sympathy with this aspect of his work and outlook. Only two volumes of the *Annals* were published. He had been a Vice-President of the Chemical Society, but at the Physiological Society was involved in polemical discussions. In these one may suspect Thudichum to have been right in chemical detail but narrow in outlook. In spite of his work, incidents such as these and such as his criticism of Kühne were a disservice to the furtherance of chemistry in physiology and medicine. They may contribute to explaining how Thudichum had no immediate successors. He was further isolated in that his medical practice was in a quite different specialty from that in which he did his major research. At least three of four people had collaborated in his work, but he appears to have had little opportunity for establishing a teaching laboratory, or perhaps by choice to have put his energies elsewhere. A wider, university atmosphere might have corrected his dogmatic and polemical tendencies.

In these circumstances it is understandable that Thudichum developed others of his many interests. Since the 1870s he had been concerned with the analysis of wines, making reports to the Pure Wine Association, London. A paper in 1870 has the intriguing title "On wines, origin, nature, analysis and uses; with special reference to a new alcoholic drink made from tea". In the 1890s, his development of this theme is seen by his books on food and wine (Table II). He also continued in medical practice. When in 1901 he published a German version of his book on the chemistry of the brain, there was little to add to his work of twenty years before. In one sense this is a measure of the magnitude of Thudichum's contributions; in this field he had worked assiduously even though he did not supersede the techniques of his predecessors. Here we come to a general point in the development of the sciences. In one sense biochemistry developed from the organic chemistry of the time of Liebig. In another sense it represented a sharp break, a refreshing and inspiring new way of approaching chemical problems in living organisms. There are few better demonstrations of this than the life of Thudichum.

I am greatly indebted for assistance given me at the Libraries of the Royal College of Surgeons, the Wellcome Foundation, and the National Institute for Medical Research.

## REFERENCES

BOWMAN, J. E. (1855) A Practical Handbook of Medical Chemistry. 3rd edit. London.
CHITTENDEN, R. H. (1930) The Development of Physiological Chemistry in the United States. New York.
DUNCUM, B. M. (1947) The Development of Inhalation Anæsthesia. Oxford.
FOURCROY, M. (1790) Elements of Natural History and Chemistry. London.
MCILWAIN, H. (1955) Biochemistry and the Central Nervous System. London.
—— (1958) In: History and Philosophy of Knowledge of the Brain and Its Functions. Edited by F. N. L. Poynter. Oxford.
Obituary (1901; anon.) *Brit. med. J.*, ii, 276.
PAGE, I. H. (1937) The Chemistry of the Brain. Springfield, Illinois.
PARIS, J. A. (1825) The Elements of Medical Chemistry. London.
ROSENHEIM, O. (1930) *J. Soc. chem. Ind., Lond.*, **8**, 238.
SUDHOFF, K. (1932) *Nachr. giessen. Hochschulges.*, **9**, 33.
THUDICHUM, J. L. W. References are included in Table I (*see* p. 127); a complete or almost complete bibliography is at the library, National Institute for Medical Research, London.

## BOOK REVIEWS

**Anatomy for Nurses.** By D. V. Davies. (Pp. ix + 371; illustrated; 20s.) London: The English Universities Press. 1957.

As noted in the preface, "This volume is intended for nurses . . . to cover the syllabus in anatomy as set out by the General Nursing Council for the Preliminary State Examination". The work achieves its purpose, and the nurse who has digested its contents will have a good working knowledge of the anatomy of the human body. The author writes simply and clearly and has succeeded in avoiding much inappropriate detail. More still might, however, have been omitted with benefit, e.g. the foramina of the base of the skull, the complete list of names of the carpal and tarsal bones, the detailed classification of joints, and some of the details of intracerebral anatomy. In certain sections, the anatomy is made clearer by a discussion of function, the best example being the reproductive system. Perhaps the author is seeking to stimulate the authorities responsible for the education of nurses into considering the whole of anatomy on a functional basis, and merging it with physiology into a common subject. If so, most educationists will wish him good luck with his efforts. But like all who try to write sound but simple textbooks for nurses, the author will have to breach the Maginot Line constituted by Sister-Tutors and fortified by tradition.

**Fluid Balance Handbook for Practitioners.** By William D. Snively, Jr., M.D., A.A.G.P., and Michael J. Sweeney, M.D., A.A.P. (Pp. xix + 326; illustrated. 51s.) Oxford: Blackwell Scientific Publications, 1956.

The problem of "Fluid Balance" cuts across many established boundaries between medicine and surgery and its proper management requires considerable knowledge of basic physiological facts as well as clinical judgment. A simple handbook on this subject would unquestionably be of great interest and value. It is, however, a notoriously difficult subject to present to the uninitiated and an even more difficult problem to try at the same time to clarify and consolidate the information of those who have made a special study of some medical or surgical aspect.

The general plan of this book is excellent. It proceeds from Foundation Facts to Clinical Diagnosis and then to Therapy including practical details of administration and finally illustrates the whole theme by analysis of clinical cases. It is a gold mine of factual information, but unfortunately, the reader must be prepared to sift this gold from a large dross of irrelevance and repetition. Similarly the language which may be suitable for contemporary transatlantic readers is strangely incongruous to us. For instance, "A century and a half ago, a strange German religious sect, the Rappites, founded the community of Harmonie on the banks of the Wabash. They built well and their sturdy, ivy-covered brick buildings still stand. Their leader was George Rapp, and therein lies our tale, for the name RAPP spells out the first letters of the end organs which provide automatic normalization or homeostasis of the fluid volume, electrolyte concentration and electrolyte composition of the body fluids. These homeostatic controls include the Renal, Adrenal, Pituitary and Parathyroid mechanisms. They are key units of a fantastically complicated regulatory system which puts man-made automation to shame". Again the effort to maintain simplicity not only makes several of the diagrams unnecessarily elaborate, but results in this sort of statement "If the pathologic state results in an increase of carbonic acid, a carbonic acid excess results." Again the figure to illustrate the clinical picture of Calcium Deficit has on it under a heading "Clinical History" a list of sixteen clinical diagnoses with no further indication as to how these conditions could bring about calcium deficiency. This endeavour to make each figure all inclusive defeats its own object of simplicity. It may, of course, be useful as a reference book for someone faced with an unfamiliar problem. No doubt the authors armed with a fluid imbalance analysis sheet (Table 8), laboratory values useful in diagnosis (Table 1, Chapter 14) and the daily fluid balance sheet (Table 2, Chapter 14) are in an excellent position to deal with problems requiring an urgent solution. Indeed the final analysis of clinical cases in Part 7 would seem to substantiate this claim. However, there are few in this country who will have the patience to assimilate facts presented in this manner.

**Recent Outbreaks of Infectious Diseases.** By S. Leff, M.D., D.P.H. (Pp. xii + 408. £1 15s.) London: H. K. Lewis & Co. Ltd. 1957.

Dr. Leff has followed the example of Greenwood in directing this book on epidemics not only to medical men but also to other health workers and to the public. In his classic work on "Epidemics and Crowd Diseases" Greenwood argued that the discussion on things assumed to have happened did happen needs logic and common sense, of which the

medical profession has no monopoly. Epidemiology perhaps alone among the medical sciences requires little clinical or technical knowledge to be understood. This is fortunate as the control of epidemic disease depends increasingly upon the intelligent co-operation of laymen, for whom there are few appropriate written sources of information. In his choice of outbreaks and most readable accounts of them, the author demonstrates that his subject can be fascinating for readers with or without medical training.

The change that is taking place in the relative importance of virus and bacterial disease is reflected in the fact that rather more than half the book is devoted to smallpox, poliomyelitis, Q fever, psittacosis and Bornholm disease. The smallpox outbreaks are particularly well described and lead to an excellent summary of lessons learned, but the two outbreaks of poliomyelitis selected might be considered atypical and the conclusions unjustified. Outbreaks of enteric fever and food poisoning occupy a further large section, to which one due to *Cl. welchii* would be a useful addition. The remainder of the book deals briefly with diphtheria, and, somewhat surprisingly, lead poisoning and atmospheric pollution. One would be happy to see a slight alteration in the title and the inclusion of further outbreaks of non-infectious disease as interesting as that of lead poisoning in Rotherham.

A useful service has been performed in bringing together many notable epidemics. The descriptions are lively and readable, and are followed by some excellent comments, particularly on practical and administrative aspects. In some sections, unfortunately, the epidemics occupy a secondary rather than primary place, being reduced to the rôle of illustrations of an epidemiological argument. The preliminary remarks on the clinical, and bacteriological features of some of the diseases are unduly long and include unnecessary technicalities. It is probably impossible for one volume to be both textbook and collection of detective stories, and the main defects of this book result from failure of the author to keep a weakness toward textbook writing in check. It is nevertheless well worth reading.

**The Clinical Application of Antibiotics.** By M. E. Florey, M.D. Volume III Chloramphenicol and the Tetracyclines. (Pp. ix + 393; illustrated. 84s. 0d.) London: Oxford University Press. 1957.

The purpose of this book is to evaluate critically the data on which the present use of antibiotics is founded. Four antibiotics are covered: chloramphenicol and the three members of the tetracycline group—chlortetracycline (aureomycin), oxytetracycline (terramycin) and tetracycline itself. Each antibiotic is dealt with under three main headings. The first chapter for each gives general considerations, then the range of antibacterial action, the complications of therapy, the main results of clinical trials and methods of administration. The second chapter deals with treatment of diseases due to specific organisms and the third with the treatment of diseases considered by systems, age groups or sex. There is an additional very short chapter on the effect of chlortetracycline on growth, thus making 13 chapters in all.

In discussing a book packed so full of important facts, it is only possible to select a few features for special comment. Under each antibiotic tables are given showing the antibacterial activity as judged by *in vitro* sensitivity tests on as wide a sample of organisms as possible. An important section in the part devoted to chloramphenicol is the discussion of the blood changes which have been attributed to the drug. The evidence for its toxicity is well and fairly presented and sensible conclusions are drawn about its use. The treatment of the tetracyclines was clearly a difficult problem to which the author has devoted a good deal of thought. It must have been difficult to decide whether to deal with the various aspects of the clinical use of all three antibiotics together or, as the author has done, to treat each of them separately. Either method has disadvantages. The method adopted, though perfectly clear in a purely factual sense, leaves the reader with a bewildered feeling that there is very little to choose between the three tetracyclines and that what is said about one of them could be said about another. This of course is broadly true and is, in fact, explicitly stated in the Conclusion on p. 335. But it is also pointed out on the same page that there are a few specific differences between the three tetracyclines. Yet there is no critical account of the possible importance of these differences nor of the indications which might in special cases justify the use of one tetracycline rather than another. This would have been achieved more easily if, under the heading of each disease or system, all three antibiotics had been dealt with one after the other and then compared.

The book is well produced and there are useful tables, graphs and plates illustrating important features—for example, temperature charts or photographs showing the response of patients to treatment. It is unfortunate in a book of this quality that there are many errors in the references. These are noted in a special list at the beginning of the extensive bibliography. The book gives a full account of the state of our knowledge up to June 1956 and will be of great value both to clinician and laboratory worker.

[*Continued on p.* 135

**Your Baby and You.** By Dr. Winifred De Kok. (Pp. 221; illustrated. 2s. 6d.) London: Pan Books Ltd. 1957.

This is a book which gives a great deal of useful knowledge in a most concise and readable manner. The style is cheerful and practical and chapters well arranged. The early chapters discuss the beginning of pregnancy and give practical advice on making arrangements for confinement and the monetary grants available. Advice on the care of the body in pregnancy is good and the description and illustration of exercises clear.

The description of suitable clothing for the expectant mother is very helpful and the advice on baby clothing is very practical. The ailments of pregnancy are set out under clear headings, which are easy for reference and should be very helpful to a pregnant woman. The organs of reproduction and the physiology of labour are very clearly described and in a manner that should be quite acceptable to the young lay mind.

The advice to fathers shows Dr. De Kok's experience of dealing with young expectant parents, and the many problems which seem so large, but are easily solved with a little common sense.

The centre of the book has some delightful photographs to illustrate baby care in the early weeks of life—the advice is given here in a practical but humorous manner.

In the chapter on artificial feeding, the use of Milton for cleaning bottles and teats is mentioned. This is such a simple and efficient method that it seems a pity not to have given it complete and in correct detail instead of as a partial addition to the boiling bottles.

The latter part of the book should make a most complete guide for a young mother. Feeding is dealt with from breast feeding to full diet. The types of food necessary are given and also the management of the child if it does not feed well at any stage.

The behaviour both good and bad of children is most sensibly explained and the correct method of overcoming difficulties and apparent bad habits.

Vaccination and immunization are recommended in a manner which should appeal to most mothers.

Whilst reading this book one has the feeling that Dr. De Kok must have a great deal of practical experience and writes with a wonderful insight into the problems of young mothers. Her professional knowledge has becomes a background for her great and very human interest in mothers and babies which has caused her to write a book which can be recommended to any expectant mother as being most readable and full of sound advice.

**Synopsis of Tropical Medicine.** By Sir Philip Manson-Bahr. (Pp. xiii + 287; illustrated. 22s. 6d.) London: Cassell. 1957.

Sir Philip Manson-Bahr first published this useful little book in 1943, since which time there has been a second edition in 1952. This third edition is notable for the addition of a new section devoted entirely to listing the drugs and antibiotics used in the treatment of tropical diseases, together with the indications and dosages.

The bulk of the book, of course, is the author's well-known, painstaking synopsis of tropical diseases; the geographical distribution, epidemiology, ætiology, pathology, clinical features, diagnosis, treatment and prophylactic measures are among the many aspects covered. In addition to those diseases directly attributed to a variety of organisms ranging from viruses to helminths, there are also included sections on the nutritional and climatic factors affecting the health of man in the tropics, animal and vegetable poisons, and infestations by arthropods and leeches.

The enormity of the information contained in one relatively small volume has naturally necessitated the use of a rather drastic note-form type of presentation. It is unfortunate that some errors have escaped notice: thus it is rather confusing to be told on page 8 that the incubation period for malaria in man is seven to nine days while the figure given on page 10 is simply ten days. Again, the sudden mention of *Plasmodium inui* in the midst of a discussion on the differences between the pre- and exo-erythrocytic stages of human plasmodia might startle readers with little (or rusty) protozoological background. There is no reference to the fact that *P. inui* is a monkey parasite which is not transmissible to man and the impression is unfortunately given that *P. inui* must be included here because it represents a fifth human *Plasmodium!*

While most of the illustrations in the 8 Plates are good, some leave much to be desired. Those of intracellular aggregations *Leishmania* in Plate III, for example, could be taken for a poor representation of almost any intracellular organism, e.g. *Toxoplasma* or *Histoplasm.* There is also an inversion in the labelling of the drawings of this plate (Figs. 3 and 4): developmental, flagellated forms of *Leishmania* are labelled "Parasites enclosed within splenic pulp cells . . ." and vice versa.

Finally, the zoologist will probably be distressed by the implication of the heading "Arthropod, Fly and Leech Infections", on page 182, that flies are not arthropods!

Such errors as the above, however, are virtually insignificant when weighed against the

undoubted great value of this encyclopædia of tropical medicine. Sir Philip's book should find a place in the pocket of all medical men, as well as the parasitologists, in the tropic

**The Effects of Arts, Trades and Professions on Health and Longevity.** By Charles Turner Thackrah with an introductory essay on his life, work and times by A. Meiklejohn. (Pp. 50 + 238; illustrated. 25s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

Charles Turner Thackrah must have been a remarkable man. His short life lay between the years 1795 and 1833, during which he achieved much. He lived in an age of great men, and was himself much influenced by his teacher, Astley Cooper, who had been a student of John Hunter. Qualifying at the earliest age possible at that time, namely at 21, he started practice in his home town of Leeds and was very shortly contributing to the even then ever-increasing volume of medical literature.

His chief claims to fame are the part that he played in the establishment of Leeds Medical School, and the production of his book entitled "The Effects of Arts, Trades and Professions in Civic States, and the Habits of Living, on Health and Longevity".

The story of his achievements is admirably told by Dr. Meiklejohn, and is made entertaining by the light that he throws on Thackrah's character. In fact the whole of the biographical essay makes excellent reading.

The main purpose, however, of the book is to reprint the second edition of Thackrah's chief work, and this in itself is eminently well worth while. Thackrah was the first man to collect together information about the effects of trades and occupations on a man's health and expectation of life, and thus to lay the foundations for prevention of disability, not only in industry, but also among the professional and leisured classes. The fact that there is nothing considerable that will surprise a modern reader of his pages emphasizes how much he was in advance of his time, and this will be seen to be true in many things, not the least being his appreciation of the importance of posture in leading to disability. His wisdom is demonstrated by his grasp of his problem as a whole, and his practical good sense is displayed by his insistence, oft repeated, on reasonable standards of living with adequate exercise and the avoidance of excesses.

This book should have a wider appeal than just to those who are interested in medical history, as in it can be read the thoughts of the enquiring, intelligent mind of a man who, living well over a hundred years ago, reached conclusions which have much point and relevance in this present day.

**An Atlas of Muscle Pathology in Neuromuscular Diseases.** By J. Godwin Greenfield, M.D., G. Milton Shy, M.D., Ellsworth C. Alvord, Jr., M.D., and Leonard Berg, M.D. (Pp. ix + 104; illustrated. 45s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

The pathology of diseases of the musculature has never been regarded as a simple problem or even a straightforward one. Study of the stimulating Atlas will leave the reader in no doubt but that the subject is vastly more complex than he ever imagined. Indeed, the authors are explicit in their appraisal of the mysteries of their task. Gloomily they assert that at times one wonders whether a muscle biopsy is really helpful. But they finish in a more optimistic key. They discard a great deal of dead wood and in doing so they sedulously avoid such terms as "degeneration", "atrophy", "regeneration" and "necrosis" which, as they point out, imply more than they describe.

A new nomenclature for dealing with the structural changes is therefore adopted. The first part is concerned with these histo-pathological reactions. The text is kept commendably brief and clear, and the argument is presented mainly by way of a rich series of beautiful illustrations, many of them in colour. In the second part of the book, the authors attempt to formulate a clinico-pathological correlation. This proves a difficult undertaking for even a clinical classification of neuromuscular diseases turns out to be a tentative and not altogether satisfying matter. We are interested to discover that there exist important discrepancies between clinical data and histological observations. It is obvious that the subject of neuromuscular disorders is still a very imperfectly documented chapter in neurology. The authors have done well in presenting so succinctly a fascinating *aperçu*. It will surely stimulate practising neurologists and their pathological colleagues to explore more deeply into these poorly charted waters.

**The Clinical Examination of Patients with Organic Cerebral Disease.** By R. Klein, M.D., and W. Mayer-Gross, M.D., F.R.C.P. (Pp. xiii + 96; illustrated. 15s.) London: Cassell & Co. Ltd. 1957.

There is admittedly a need for a clinical manual dealing with the systematic examination of a patient with organic affections of the brain. The very fact that no such treatise has been undertaken up to now is possibly significant in itself. Various experienced neurologists,

[*Continued on p.* 137

with particular interest in a knowledge of problems of highest level cerebral dysfunction, have been known to have pondered the matter seriously only to have decided finally that the subject is best avoided. The two present authors are therefore to be congratulated upon their courage in grasping this particular nettle. Their armamentarium of clinical tests is a good one but perhaps they have tended to gloss over some of the difficulties—which are in themselves an integral manifestation of the disordered behaviour in their cases. For example, the question of what a patient can do or cannot do in a given test-situation tells us only a little. What is much more significant is the way the patient goes about the task. This cannot be adequately evaluated without a full-dress description. Case-taking must therefore be of necessity a laborious and detailed procedure, and short-cuts, schemata, and questionnaires are inadequate. The patient's hesitancies, inconsistencies, slowness, changes of mind, perplexity, and display of emotion are much more meaningful than an eventual correct answer or performance. This applies to the patient with aphasia, apraxia, "agnosia", and indeed almost any other cerebral disorder of perception or of symbolic thought.

These then, in the briefest of terms, are some of the pitfalls attendant upon the examination of patients with organic cerebral defect. As the clinical snares have not been made clear by the writers at the very outset, the value of the present schema of tests suffers. It is uncertain for whom the manual is written; if for an undergraduate it is too recondite, and if for a neurologist it is inadequate. Perhaps it can best be summarized as being written for young psychiatrists by psychiatrists of experience.

As far as they go, the clinical procedures form a useful *aide-memoire*, for complex and manifold as are the manifestations, they may elude the attention of those who do not handle such patients every day. Certain errors and points for criticism can be picked up here and there; e.g. Koh's for Kohs' blocks; and Bey for Bay. The English style is halting, and in places it transgresses the canons of accepted usage. The term "residual utterance" is an unorthodox one in neurology. The insecure status of the agnosias is perhaps not sufficiently stressed. Disorders of tactile perception are sketchily dealt with, and although tactile agnosia is discussed, the commoner astereognosias are by-passed. There is a useful bibliography but with perhaps undue emphasis upon the German literature.

**A Manual of Human Anatomy.** By J. T. Aitken, M.D., G. Causey, M.B., F.R.C.S., J. Joseph, M.D., M.R.C.O.G., and J. Z. Young, M.A., F.R.S. Vol. III—Abdomen and Pelvis. (Pp. viii + 135; illustrated. 12s. 6d.) Vol. V—Central Nervous System. By J. T. Aitken, M.D., D. A. Sholl, B.Sc., and J. Z. Young, M.A., F.R.S. (Pp. vii + 140; illustrated. 12s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

With their companions, these volumes provide a complete guide to the dissection of the human body. They are brief and factual and cover reasonably adequately the needs of the medical student in the dissecting room. As a purely factual and limited description of human anatomy they must be praised, and their brevity is highly commendable. The student dissecting for the first time might well find the book helped him very little in the identification of structures in the body and would need a great deal of personal supervision and assistance to make his dissection comprehensible. In the part devoted to the abdomen and pelvis the illustrations are good and there is a practical guide to surface anatomy. The central nervous system is more comprehensively described and notes on its development in this type of manual seem ectopic. Much of the material here is devoted to a description of slides from one particular school, and the text would need some revision before it is generally applicable. The series is most attractively produced in a form suitable for the dissecting room, and represents a notable advance in the simplification of anatomical teaching.

**Medical Negligence.** Being the Laws of Negligence in Relation to the Medical Profession and Hospitals. By the Right Hon. Lord Nathan, P.C. (Pp. xxxii + 218. 35s.) London: Butterworth & Co. (Publishers) Ltd. 1957.

Lord Nathan, in his preface, gives two reasons for this book. "In the first place, I have sought to present, in a form which it is hoped will be useful to the legal practitioner who is called upon to deal with such matters, an objective and comprehensive statement of the law relating to the liability of medical practitioners and medical institutions for professional negligence." Your reviewer, writing as a lawyer, agrees that he has succeeded in his first purpose. The references to the numerous cases of medical negligence in the courts of the Dominions and of the United States of America add to its utility to the lawyer. It is comparative law at its best. He explains the second purpose in the following paragraph: "At the same time I have been anxious to avoid, as far as possible, the unattractive characteristics of so many legal textbooks—obscure language, voluminous footnotes and the rest—in the hope that the book may prove acceptable to members of the medical and nursing professions and to hospital administrators as providing in a readable form *some guidance*

*on the nature of their professional responsibilities and the risks which affect them in the course of their work.*" (The italics are mine.)

The author in Chapter I—Introductory—on pages 4 and 5 makes certain observations regarding medical negligence actions in general and correctly assesses the three main factors for the very substantial increase in the volume of such actions. They are the introduction of the National Health Service Act, which has effected a subtle change between the medical man or hospital and the patient, the introduction of the Legal Aid Act and the modifications in the Law relating to the liability of hospitals for the acts of their staff (Chapter 5). Your reviewer, writing as a doctor, finds it an illuminating admission by the author, whose political allegiance he knows quite well, that the National Health Service Act has altered the doctor-patient and hospital-patient relationship. The sting is in the tail of this introduction. "It is perhaps inevitable that there should from time to time be cases in which the standard of skill and care exacted by the judges may appear to the medical profession to be excessively high." As a doctor, your reviewer strongly disagrees with the author that "it may be some consolation to reflect that a Court which exacts a high degree of skill and care from a particular defendant is in effect paying tribute to the high standards maintained by the medical profession as a whole."

The *professional responsibilities* of the doctors have not changed since the days of Hippocrates, modified by the Declaration of Geneva, which was evolved by the World Medical Association in 1951. The *risks* which affect them in their work have changed. It is not true to assert that there has been no change in the general law of negligence as it affects the medical profession. I quote Croom-Johnson, J., in *Best v. Samuel Fox & Co* (1950), 2 All. E.R. 798: "The law of England is a living law. It develops and must develop according to change in social life and social outlook." Lord Justice Denning recently asserted that the law is simply a means, albeit an uncertain process, whereby society works out its purposes. In the last fifty years we have seen revolutionary changes in the social structure of this country, especially since the end of the last war. Inevitably the enormous growth in the medical services has made them become of increasing importance in the social structure. The creation of the Welfare State has produced legal problems which are inextricably intertwined with this era of profound change. Where does the doctor stand in this elaborate and uncertain legal process whereby society works out its purpose? He now lives in a world of greater legal risks by reason of the present nature of the judicial process which has enlarged and extended the scope of medical negligence by the very exacting and often onerous standards of medical care and skill.

In spite of these criticisms I must congratulate the author and his collaborator on a concise and well-written book on a very important subject. The case law is extensive and the salient points in the judgments clearly emphasized. I strongly recommend all doctors and hospital administrators to read it. The book has a very useful index.

**Principles of Renal Physiology.** By Homer W. Smith, A.B., Sc.D., M.S. (Pp. x + 237; illustrated; 40s. 0d.) Oxford University Press. London: Cumberlege. 1956.

This little book of some 237 pages gives the current views of renal physiology in a condensed form.

The author gives the anatomy and an excellent short historical note on the theories of renal function before starting to deal chapter by chapter with each of the functions of the kidney. The various principles governing the determination of filtration and reabsorption rate, and renal plasma flow are given in detail. The latter chapters are mostly concerned with the specific problems affecting the kidney, such as water and electrolyte control, together with the formation of ammonia and control of the acid-base equilibrium. In fact all the aspects of the kidney are fully covered.

In the Appendix, which is the most interesting section of the book, a description of the structure of the glomerulus, proximal and distal tubules, as seen by electron microscopy, is given. This is particularly well done, and clarifies the previous literature on the subject. The analytical methods used for determining the renal clearance, filtration rate, and renal plasma flow are given in full with alternative methods.

The principal difficulty of this book is that it is not quite clear for whom the book is intended. In this country the pre-clinical student would hardly find it necessary to go into such minutia of renal function as given here. Nevertheless, it may well fill the want of the postgraduate student who wishes to bring his knowledge up to date, particularly those sitting for the Membership of the Royal College of Physicians—or those who wish to study current renal problems before undertaking research.

At the end of each chapter a problem is set to the student, which is perhaps a little irritating, but no doubt will be found useful by the student sitting for an examination. At the same time the list to guide future reading and the analytical methods will prove valuable, and will serve as an introduction to a most intricate subject, since the subject matter is clearly put out and easily assimilated.

# Section of Epidemiology and Preventive Medicine

President—IAN TAYLOR, M.D., M.R.C.P., D.P.H.

[*October* 18, 1957]

## SYMPOSIUM ON OPERATIONAL RESEARCH IN THE NATIONAL HEALTH SERVICE

Dr. J. N. Morris (London): *Introduction*

The subject of this symposium may be defined as *the scientific study of the working of the National Health Service with a view to its improvement*. "Operational Research" was invented before the war in connexion with radar, to analyse its translation from theory to practice—i.e. what actually happened when radar was tried out in real life. An institution like the National Health Service, it is safe to assume, does not do all it is supposed to do, and does things it was never intended to do. Obviously there is need and scope for investigation but, so far, there is far less of this than there might be. Meanwhile, operational research has developed rapidly in industry and elsewhere, and in the process has acquired some particularly striking statistics. There is a lot to be learned from these studies: for example, the problems of economic stocking and the flow of materials through a factory, or of the flow of iron ore from ship to furnace, or of traffic on road and roundabout have, technically, much in common with medical-administrative problems already tackled on the flow of out-patients in general hospitals (Welch and Bailey, 1952) or of inpatients through mental hospitals (Kramer, 1957).

Three stages may be described in operational research. *First*, the estimation of needs; *second*, analysis of services in action; *third*, appraisal or evaluation of their success. All these present serious difficulties, but it is one of the advantages of this type of study that modest and simple inquiries may yield immediately useful information, useful to the administrator and to the community in helping them to make the right decisions in particular situations. It is, however, important to ask questions that are founded on some knowledge of what the Health Service is about; too little of such appreciation reduces the value of some of the studies that are being made.

The classic example of estimation of need in advance is that by the Social Survey on the Medresco Deaf Aid (Wilkins, 1949) to which Mr. Moss will refer. There is little doubt that some of the violent criticism which the National Health Service had to meet in its early years could have been reduced, or even avoided altogether, if similar studies had been done on the need for spectacles, dentures, &c., so that the government could have used and publicized more realistic estimates of needs and costs. To-day there are many difficult questions. For example: supposing maintenance anticoagulant therapy is proven of value in coronary heart disease, what clinical and pathological service will be necessary to discharge the responsibilities of the National Health Service? How are the needs for cardiac surgery assessed at the Ministry? Presumably they will differ regionally and locally, for example with the incidence of juvenile rheumatism some years ago. What are the unmet needs for specific treatment of depression in the elderly? In general, with mental illness no realistic assessment of needs is possible as yet; which perhaps does not matter too much since we are a long way from being able to satisfy demands that are already vocal and pressing upon us. In this field, even more than in physical disease, it must be expected that the provision of services will uncover needs, "create" demand, change public perception of what is tolerable (Koos, 1954).

In the analysis of actual services, Dr. Martin will describe the use made of the experiment of opportunity offered by a new housing estate. Dr. Lee will give an example of the kind of difficulty that is involved in providing a meaningful statistical analysis of hospital staffing (Lee *et al.*, 1957). How far do the exceedingly important factors about which there is not, and often cannot be, statistical information affect the picture presented of gross inequality in the staffing of teaching and non-teaching hospitals?

Attempts to appraise the quality and to evaluate the success of services present most difficulty, and often go by default in favour of studies of bed-turnovers, man-laundry-days, &c. (Lee, 1958). The methodology may be readily available, e.g. in clinical therapeutic trials and the actuarial life-table. To mention only two instances, as yet there is little evidence that mass tonsillectomy is worth while—or has been abandoned; and the child guidance movement is still little more than an act of faith.

In view of the changing character of health problems, of medicine, and of health services,

it might be expected that a great deal of operational research would be going on. This is not the case. The Guillebaud Committee (1956) recommended that the development of these inquiries should be based on the Ministry of Health. Although the recent development of an energetic and enterprising Statistical Division at the Ministry is much to be welcomed, it is doubtful whether the Ministry is a suitable centre for many of the studies. The Ministry is too involved in problems of medical politics and finance to be a good base for the research into, say, the quality of general practice. Moreover, many of the problems needing study cross government-departmental boundaries, and a Ministry of Health research group would be badly placed to examine the problems of industrial medical services. Great foundations are interested in this field, and the King's Fund and the Nuffield Foundation have made notable contributions; the latter's researches (1955) into the design and functions of hospitals, it is encouraging to learn, have now been placed on a permanent basis. However, it is clear that the main responsibility for operational research in the future will devolve on the academic departments of social medicine in collaboration with their colleagues in the social sciences. It must be faced therefore that these inquiries inevitably raise controversial issues which may be viewed very differently by the administrator in the government department and the academic investigator outside. It would be idle to fancy that these differences can easily be reconciled. This is merely one aspect of a central problem of our times, the relations of science with government.

The improvement of the National Health Service is an objective which commands general support and there is probably more general agreement about it than on any other comparable issue of social policy. Operational research, which means for the most part an application of epidemiological methods (Morris, 1957) has a part to play in attaining economy and efficiency, in the optimum use of scarce man-power. Above all, it can help in discharging the responsibility of the medical profession for the quality of medical care.

## REFERENCES


Guillebaud Committee (1956) Report of the Committee of Enquiry into the Cost of the National Health Service. Para. 699. H.M.S.O. London.

Koos, E. L. (1954) The Health of Regionville. New York.

Kramer, M. (1957) *Amer. J. publ. Hlth.*, **47**, 826.

Lee, J. A. H., (1958) In preparation.

——, Morrison, S. L., and Morris, J. N. (1957) *Lancet*, ii, 785.

Morris, J. N. (1957) Uses of Epidemiology. Edinburgh.

Nuffield Provincial Hospital Trust and the University of Bristol (1955) Studies on the Functions and Design of Hospitals. London.

Welch, J. D., and Bailey, N. T. J. (1952) *Lancet*, i, 1105.

Wilkins, L. T. (1949) Survey of the Prevalence of Deafness in the Population of England, Scotland and Wales. The Social Survey, Central Office of Information, London.


**Dr. J. A. H. Lee** (London) read a paper entitled: "Fatality from Three Common Surgical Conditions in Teaching and Non-Teaching Hospitals" (*see* Lee, J. A. H., Morrison, S. L., and Morris, J. N. (1957) *Lancet*, ii, 785).

**Dr. F. M. Martin** (Edinburgh): *Some Problems of Health and Medical Care on a New Housing Estate*

This paper presents some of the results of a study of a new housing estate carried out by a group of workers in the London School of Hygiene under the direction of Dr. J. H. F. Brotherston.

The estate which stands in Hertfordshire is one of a dozen out-county estates built by the London County Council during the post-war years. It contains more than 4,000 families and has a total population of between 17,000 and 18,000. Most households, as is common in new housing areas, consist of a married couple in their thirties and a pair of children of school or pre-school age. About two-fifths of the entire estate population at the time of our enquiries were below the age of 16 and only 12% were over the age of 45. Two principal factors determined a family's degree of priority on the housing waiting list at the time the estate was built. The more important of these was overcrowding and the other was certificated ill-health. We found that medical certificates in support of an application for re-housing had been submitted by half the families living on the estate. These had all been scrutinized by the Council's Medical Officers and four-fifths of them had been approved. The most common diagnostic groups as indicated by the certificates were lower respiratory conditions, nervous disorders, tuberculosis and upper respiratory disease, accounting respectively for 17, 14, 12 and 8% of all certificates. The use of medical judgments seems to derive less from knowledge of the beneficial effects of re-housing than from the need to employ a system of priorities among cases which cannot on ordinary housing grounds be differentiated one from another, by applying a criterion

which, though often of dubious relevance, carries an authority which our culture places beyond question.

The population was drawn predominantly from the ranks of skilled manual workers, and although it carried only a thin layer of black-coated workers (perhaps 10% of the total) its complement of semi-skilled and unskilled manual workers was proportionately smaller than that of London or of the country as a whole. It is notoriously difficult to secure accurate information about incomes but our evidence, such as it is, strongly suggests that the families who moved to the estate were on the whole a good deal better off than the general run of the Council's applicants for new housing. It is, in short, a group which might be expected to adapt itself to a lower middle-class pattern of residence, of income distribution and of family aspirations more easily than many other segments of the working class, though by no means painlessly.

Can any distinctive features be observed in the sickness experience of the estate population or in their usage of health services? In purely quantitative terms the volume of demand for the general practitioner's services does not differ very much from that established for urban practices by Backett, Logan and others. The reduction in the consultation load arising from the virtual absence of old people from the estate is counterbalanced partly by the large number of children and partly by the sizable number of people re-housed on the grounds of ill-health. Infectious diseases play an exceptionally large part in the work of the general practitioner as do symptomatic and ill-defined conditions. Many of the latter appear to have a large psychological element. Thus anorexia, debility and undue fatigue, and headache are all more common than in any of the twenty-six practice-years studied by Logan, while other conditions such as insomnia and vertigo are well in the upper half of the range of consultation rates which Logan reports. Among the digestive conditions it is interesting to see that although consultation rates for gastric ulcer and for dyspepsia correspond very closely with expectation on the basis of age and sex, the rate for duodenal ulcer is nearly three times the expected figure and is exceeded in only one of Logan's twenty-six practice-years. Migraine among the diseases of the nervous system and urticaria, hay fever and asthma among the allergic conditions, all have consultation rates which fall in the top third of the range observed by Logan. What these conditions have in common, of course, is that they are all fairly strong candidates for classification as psychosomatic. The frank psychoneuroses all had consultation rates above the expected figures—twice as high in the case of anxiety neurosis.

It is difficult to say very much about distinctive features in the use of hospital services by people living on the estate as most published studies do not relate hospital admission or out-patient consultation rates to any defined population. The mental hospitals are an honourable exception and here it has been possible to compare admission rates over a six-year period with a national standard. During the whole of this period admissions were about 50% higher than would have been predicted on the basis of age and sex composition. Comparison with Greater London rather than national admission rates reduces the discrepancy but only slightly. On the other hand, no allowance has been made for the fact that the estate contains so few unmarried adults and so few unskilled manual workers—both groups with disproportionately high mental hospital admission rates. The observed excess appears to be due mainly to a high incidence of neurotic depression among middle-aged women.

As far as other hospital admissions are concerned there do not seem to be many outstanding features. The high—though not unparalleled—frequency with which patients were referred to hospital out-patient clinics can best be understood in terms of the impact on a group of relatively inexperienced general practitioners of a population which by definition had more than its quota of health handicaps and with no provision (except in cases of tuberculosis) for maintaining continuity of care or even for transferring essential information. In the circumstances it was inevitable that they should make generous use of consultant services if only to establish a base line.

The infant welfare services are very widely used and appear at first inspection to overlap considerably the work of general practitioners. The important and distinctive service provided by the clinic doctor was to listen with sympathy and understanding and thereby provide some substitute for the traditional supports of the family and the neighbourhood which were so clearly lacking.

New housing areas would seem to offer ideal testing grounds for experiments in collaboration between the branches of the National Health Service. The planning of the estate coincided with the planning period of the National Health Service. The London County Council reserved a large site for a health centre and the Hertfordshire County Council planned an elaborate structure to accommodate general practitioner and local authority services. However, no doctors practising in neighbouring areas were prepared to commit themselves in advance to paying substantial rents for consulting rooms in the

new centre, and the plan was dropped with no more modest alternative being provided. Thereafter, local authority and general practitioner services developed independently for a few years and with minimal contacts until in due course the suggestion was put to both groups that they might consider investing in new premises for their joint use. After long discussion dissatisfaction with grossly inadequate existing accommodation triumphed over memories of an earlier rebuff on the one hand and fears of marauding practitioners on the other. Work has begun on a group-practice building and on new local authority premises. These have been designed by the same architect in such a way that the two buildings, though legally separate, form an architectural unity.

We have been impressed by the need for special arrangements for the provision of health services on new housing estates of this kind, having regard to the size of the community, its special nature—particularly if priorities on health grounds are awarded—and the supportive functions which community services have to provide to substitute for the loss of the traditional supports of family and neighbourhood. Situations of this kind present distinctive difficulties which generally include local suspicion and hostility to the new community and a failure to recognize its problems. This is particularly understandable when services whose provisions are already inadequate or hard pressed in the face of a rising demand have these new needs thrust upon them. The administrative rigidity of the National Health Service and some of its divisions of responsibility—for example in the provision of health centres—also make it difficult to take effective administrative action in advance of the population and its demands. There are, however, some aspects of the situation which might have been turned to very good account—its fluidity in the early stages, and the malleability of behaviour produced by the lack of any clear-cut expectations in the re-housed population. It seems to us that this new estate offered to the National Health Service an opportunity for imaginative experimental planning which, so far from being grasped, was in fact scarcely even recognized.

**Mr. Louis Moss** (Government Social Survey): *The Use of Survey Techniques in Connexion with the Operation of a National Health Service*

This paper does not attempt a general review of all the possible uses of survey techniques nor even of all the past actual uses of survey techniques in connexion with public health services. It is limited to a summary account of some of the ways in which survey techniques have been used in this country on health service problems by the Government Social Survey.

We can say that, in general, survey techniques can be used to do two main things for a national health service. They can help us (1) to obtain an overall picture of the problems which the service is designed to help, or (2) to examine the efficacy of the methods and organization used to deal with any selected part of the whole field. The term "operational research" may fairly be applied to both uses.

*Survey of Sickness*

A good example of the first use is the Survey of Sickness enquiry which was carried out for the Registrar-General over many years in this country. The Survey of Sickness had two purposes. Its first purpose was to give an overall picture of the level of incapacity and the range of complaints in the population as a whole. Its second purpose was to provide a picture of the use made by those with complaints of different sections of the medical service.

The method used is to sample the whole population and, by means of direct interview in which individuals are taken through the whole range of morbidity and possible medical attention, to obtain an overall picture of what has happened in a limited period of time [1]. Broadly speaking, by means of this technique we screen the whole population. Clearly the results achieved are very closely related to the fineness of the screen used and this may vary according to the resources which are available for the work. The Cornell Medical Index, for example, applies a much finer screening process than the one used in our Survey of Sickness.

In any study of this sort the nature of the screening process should relate to the degree of detail which is thought to be operationally useful. Clearly it is not to be expected that ordinary members of the public will be able to diagnose illnesses which only thorough medical examination can bring to light [2]. The screening process which such a study carries out is therefore unlikely to be on a very profound level.

Whatever the limitations of the data for diagnostic purposes it seems to be suitable for very many purposes of organisation and administration in the public health field. The limitations of the method seem to be fairly clear. It may therefore be useful to summarize briefly what the method enables us to do that is not otherwise possible. In the first place efficient sampling can give us a comprehensive picture of the whole population, of all known illnesses and of all uses of health services in very broad terms. In this sense it covers a much wider field than data related only to those who are covered by insurance schemes

or by those who attend hospitals. It is likely to be more comprehensive and representative of the general population than information derived from doctors keeping voluntary records. Secondly, since all continuing records are likely to be limited it is very often difficult to derive detailed classifications of the patients concerned from them. For example, in trying to derive the economic group of patients covered by administrative statistics the statistician is often forced to use very broad economic indices of the district in which they live. Since Survey of Sickness data are obtained directly from patients it is possible to obtain more detailed information about the social and economic context of illnesses and use of health services. Because this information is obtained directly it can be more precise than data available from mass records. It may be said, therefore, that whilst Survey of Sickness information tends to be broad and general in the morbidity field it can be more detailed and explicit on the social and economic factors, or what might be called behavioural factors, involved in illnesses and medical attention than other forms of data. It can clearly be much more comprehensive and representative than other forms of data.

It may be asked what operational uses can be served by the information derived from this kind of survey [3]. If such a survey continues over time we can derive data which enable us to make statements about changes between two points in time. Thus Dr. Logan of the General Register Office used Survey of Sickness data to study changes in illness, incapacity and medical attention among adults in the year before and after the inauguration of the National Health Service [4]. Perhaps one of the most important contributions of this type of survey is that it enables us to see how the total amount of medical care and attention is distributed between different sections of the population. In a very useful account of the kind of data produced by the Survey of Sickness Gray and Cartwright [5] have shown that the weekly medical consultation rate per 100 persons in 1950 varied from 7·6 in those aged from 21 to 34 to 16·7 in those aged from 65 and over. Similarly, the weekly medical consultation rate varied from 8·9 per 100 persons in the higher income groups to 16·0 per 100 persons in the poorer sections of the population. They showed, too, how the rate of consultation was related to the percentage of consultations resulting in a prescription.

Survey of Sickness type data enable us, therefore, to study changes over time and, by implication, the relationship between these changes and administrative actions of one sort or another, changes in policy and so on. These changes may be studied not only in so far as they affect the population as a whole but also in terms of the sectors of the population affected. By using data about the attention received by patients we can say a great deal about the work done by doctors, the distribution of doctors' time between different sectors of the population and in relation to different forms of incapacity.

However, survey methods cannot only be used to describe existing situations; they can also help to plan developments.

*Forecasting Change*

After the National Health Service in this country was set up experience showed that demand for some of the facilities provided was much greater than had been anticipated. In only one field was an attempt made to predict the new level of demand. This was in connexion with the Medresco Hearing Aid. The M.R.C. Committee on Deafness asked the Social Survey to try to measure the prevalence of deafness in the civilian population and to make some estimate of the number of Government hearing aids likely to be required. Wilkins used the basic framework of the Survey of Sickness for his attempt to answer these questions [6]. Using a scale of questions devised by an American researcher which related social disabilities to measured hearing losses, Wilkins was able to show what proportions of the total population were likely to be suffering from different levels of deafness. By the use of additional questions he was able to make estimates of the likely demand for hearing aids on a series of different assumptions.

It is useful to continue with the same example in order to illustrate the second main contribution which survey techniques can make to the operations of a health service as a going concern.

*Studying the Use and Servicing of an Appliance*

After the Medresco hearing aid had been available for some time the Social Survey was asked by the Ministry of Health to study the use actually made of the hearing aid with a view to making any improvements which experience had shown to be necessary and possible. Gray has given an account of some of the results of this work [7]. He sampled those who had actually been issued with the aid, obtained detailed information from them about the use made of the aid and the circumstances under which it was used, and then went on to investigate a series of practical problems connected with the running of the service, such as the provision of batteries, servicing and so on.

By showing under what circumstances the hearing aid was worn Gray was able to make clear what actual working conditions the aid was having to meet. This information was

also useful in showing the conditions under which the new transistor aids would have to work. An examination of the repairs needed and the number of visits made for repair of the aids showed how much time was involved in having them serviced and the relative frequency of different types of repair.

Special meters were used by the interviewer to take readings from the batteries actually in use at the time of the interviews. It was thus possible to determine whether patients were using their batteries to the utmost. A comparison of the hours of use actually obtained with that theoretically possible if the batteries are used fairly rapidly showed that, where batteries were used only intermittently over a long period, battery deterioration resulted in appreciable loss of capacity.

With the use of information of this sort it was possible to suggest ways by which the servicing and repairs arrangements could be changed to the advantage of the patient and the economy of the service. This study I think is a classic example of operational research. I would note that the basic information came from first-hand contact with and observation of patients. The detailed questions were, of course, worked out in close collaboration with the technicians and administrators concerned with the service. In this way it was possible to ensure that the data collected would have a direct bearing on problems which were in the minds of the administrators.

*Studying the Working of a Policy*

For a further example of a study designed to check the operation of a health service activity I shall turn to a completely different field. For many years we have had a welfare foods policy and Fothergill [8] carried out a series of surveys at the Social Survey designed to show actual food intakes of special sections of the population. This he did by selecting samples of these special sections and persuading informants to weigh all foodstuffs taken in a given period. These weights were then transformed with the use of conversion tables into nutrient quantities. By use of this kind of material, it was possible to show what the facts were about the nutritional condition of the sections concerned. Within this framework it was possible to answer some questions of operational importance. For example, if the whole diets of children of a certain age were known and the nutrients derived from different kinds of foodstuff could be shown in the manner I have just indicated, then it is possible to answer the questions: Would the diets fall below necessary minimum levels if there had been no intake of welfare food? What contribution is made to vitamin-C levels by fresh fruit or by orange juice provided under the welfare food scheme? Other surveys in this field gave answers to such problems as: Which sections of the population get their welfare foods from one source rather than another? Did the change in the method of distribution of the welfare foods affect the numbers of people taking the welfare foods? [9] Which sections of the population appear to make least use of the welfare food scheme? And so on.

I would now like to give one further example in which survey techniques have been used to provide experimental evidence about the possible effects of suggested changes.

*Providing Experimental Evidence of the Effects of an Innovation*

The work of a Nuffield research group under the leadership of H. A. Goddard led to certain conclusions about the organisation of hospital nursing work. In particular it was suggested that there were many advantages to be derived from what is called "group assignment" as contrasted with the older method of "work assignment". Under "group assignment" two or more nursing teams in the ward each undertake the nursing care of a small group of patients, while under "work assignment" all the nurses in the ward perform specific tasks for all the patients. Advantages were suggested both for patients and for the training of nurses as well as in maintaining the interest of nurses in nursing duties. It seemed to be important to put these suggestions to some practical test. The Social Survey were asked by the Standing Nursing Advisory Committee to devise experiments with this end in view. The co-operation of four hospitals was obtained and appropriate studies were made in a medical and surgical ward in each of the hospitals. Briefly, the studies designed by H. W. Willcock involved before and after observations in these eight wards. A group of nurses was trained by the Social Survey in direct stop-watch observations. A sampling system was devised by which nurses' time was sampled in half hourly periods throughout the working day in the selected wards and spot observations taken at 15-second intervals. All wards were studied by this method and a detailed account thus obtained of all activities taking place in the ward, the nurses carrying them out, the time taken to carry them out, and the condition of the patient concerned. After these preliminary observations had been made the wards concerned were reorganized on a group assignment basis and the new system put into operation. When the hospitals concerned felt that the new system had been working long enough, a further week's observations using precisely the same techniques were made. Comparisons were thus possible of the

whole range of work carried out within these hospital wards before and after the new method of hospital organization. Willcock was thus able to show how the time devoted to different kinds of activities by different levels of nurses had changed. With this information as a background it was possible to see whether or not the different advantages expected from the group assignment system had been achieved. For example, Willcock showed that under group assignment there was a change in the kind of patient on whom attention is concentrated. Those in what he called "Dependency state 2: mainly a state of recovery prior to being allowed out of bed" got a great deal of the additional nursing time available under group assignment. First-year student nurses spent only 21% of their time on technical nursing procedures under work assignment but 30% under group assignment. A detailed examination of the data showed that they were not undertaking duties outside their competence.

The individual staff nurse spent more of her time under the new system with both third-year and junior student nurses: the increase was from 104 minutes per 1,000 minutes under work assignment to 154 minutes per 1,000 minutes under group assignment.

It was relevant to this study to find out how the nurses, patients and doctors felt about the new system and to consider their subjective reactions together with the objective data obtained from the time sampling studies. One of the methods by which this was done was to obtain details of complaints about their hospital stay from patients who had been in the wards during the two periods concerned. It was possible to show that the level of complaint dropped sharply under group assignment. Although the number of criticisms made under both systems was relatively small, there was a reduction of more than a quarter under group assignment. This lower level of complaint covered the whole field of complaints.

*Conclusion*

The surveys I have referred to cover a rather wide range of techniques: we have used interviewing methods, we have obtained objective data about the use of appliances from our own observations, we have persuaded sections of the population to make detailed records of their diets, and we have observed with time and motion study methods the activities of nurses inside hospital wards. This range of techniques may be surprising to those who think of social surveys only in terms of public opinion studies. I would not want for one moment to minimize the importance of opinion studies for any public service, especially one which claims to be run on democratic lines. At the same time it is clear that many of the operational problems which arise in connexion with public health services require a wider range of information. The techniques which it is right to use on each problem are those which can produce the appropriate data and this varies from problem to problem. All the data collected in the work described, however, have come from some kind of direct contact with the population concerned; none of it could have been obtained from existing records thrown up by the day-to-day operation of the service concerned. Not only must the questions asked be useful ones, their detail and ordering is of great importance, and so is the method of asking and recording [10]. The more detailed the information required the more important it is to use fieldworkers who have been trained to interview, observe and record. All the information used in these studies was obtained by the staff recruited and trained by the Social Survey.

Data are only likely to be useful for operational purposes if the questions and observations which produce them are defined in the light of operational problems and methods. For information to be operationally useful, therefore, it must derive from studies designed in close working contact with those involved in the operations. All the studies referred to here have been worked out on this basis. In this sense they are examples of the use of research methods to assist working operations.

## REFERENCES


1 STOCKS, P. (1949) *Stud. med. Popul. Subj.*, No. 2.
2 ELINSON, J., and TRUSSELL, R. E. (1957) *Amer. J. Publ. Hlth.*, **47**, 311.
TRUSSELL, R. E., ELINSON, J., and LEVIN, M. L. (1956) *Amer. J. Publ. Hlth.*, **46**, 173.
3 U.S. National Committee on Vital and Health Statistics (1953) P.H.S. Publication No. 333. Washington.
4 LOGAN, W. P. D. (1950) *Lancet*, i, 773.
5 GRAY, P. G., and CARTWRIGHT, A. (1954) *Appl. Statist.*, **3**, 19.
6 WILKINS, L. T. (1949) Survey of the Prevalence of Deafness in Population of England, Scotland and Wales. The Social Survey, Central Office of Information, London.
7 GRAY, P. G., and CARTWRIGHT, A. (1951) *Lancet*, i, 1170.
8 *see* e.g. BRANSBY, E. R., and FOTHERGILL, J. E. (1954) *Brit. J. Nutr.*, **8**, 195.
9 FOTHERGILL, J. E. (1951) The Uptake of Welfare Foods. The Social Survey, London; No. 178.
—— (1957) The Uptake of Welfare Foods. The Social Survey, London; No. 262.
10 *see* e.g. FOTHERGILL, J. E., and WILLCOCK, H. W. (1956) Interviewing and Interviewers. Readings in Market Research. B.M.R.B., London.

[*November* 15, 1957]

## SYMPOSIUM ON EVENTS IN PREGNANCY IN RELATION TO DISEASE AND DEFECTS IN THE INFANT

**Dr. Alison D. McDonald** (London):

Until recent years it was commonly believed that congenital malformations were genetically determined, but the possible role of environmental factors is now receiving more attention. Animal experiments have shown that pregnant females exposed to anoxia and to a wide variety of other agents—chemical, endocrine, dietary, actinic, and mechanical, may give birth to defective offspring. The nature and frequency of defects produced in this way are often related to the stage of gestation at which the noxious agents are administered. Some malformations undoubtedly result from arrested growth of a tissue, but as has been pointed out by Patten (1957), this mechanism does not explain those apparently due to overgrowth or failure of tissue absorption. It is still not known whether any of these animal experiments have any relevance for man, and rubella is still the only environmental agent which it is possible to incriminate. However, there has been comparatively little epidemiological study of many events in pregnancy that might conceivably be important.

Of the various insults that bring about defects in experimental animals, anoxia and mechanical stress are two which could also occur during normal human pregnancy. Though gross dietary deficiencies in times of war and famine have not apparently been associated with an increase in congenital malformations, excessive vomiting of pregnancy could result in temporary dietary deficiencies of perhaps a different nature. There is no convincing evidence that specific infectious diseases other than rubella cause defects, but the importance of less obvious infections, including those of the upper respiratory tract, has not been explored. Lack of seasonal and long-term variation in the incidence of defects, however, suggests that such infections could hardly account for a high proportion of the total.

It is probable for embryological reasons that most defects originate during the first 12 weeks of fœtal life. Retrospective investigations undertaken at the end of pregnancy are of limited use in the study of this period as a mother's recollection of events six or more months earlier is liable to be inaccurate and influenced by her knowledge of the outcome. The prospective method although laborious is free from these problems, and provides comparable information on a large number of normal births.

In a prospective study that I began in Watford and St. Albans in 1952, results of which are described fully elsewhere (McDonald, 1958) some 3,300 women were questioned at the time of booking for a confinement, about events in the first 12 weeks of pregnancy. They were then followed until the outcome of the pregnancy was ascertained. So far only defects observed at or soon after birth have been available for analysis. Many important defects will therefore have been missed, but it may be possible to have the children examined again later. In this series there were 122 congenital defects—50 somewhat arbitrarily classified as major and 72 as minor—68 spontaneous abortions, and 74 stillbirths or neonatal deaths without congenital defect.

The mothers of infants with minor defects did not appear to differ from those of normal infants in any of the factors examined. In the remaining three groups—major defects, abortions, and stillbirths or neonatal deaths—no significant difference was found in respect of a number of factors, but in others certain differences were noted. There was no indication that marked vomiting influenced the outcome, nor were events which might cause fœtal anoxia, e.g. fainting, general anæsthesia, and vaginal bleeding, more common among mothers of infants with major defects. On the other hand there was an association between vaginal bleeding and stillbirth or neonatal death. Confessed attempts at abortion and maternal injuries were equally common in all groups.

Chronic disease was slightly more common among mothers of infants with defects, but on further analysis the difference was found to be due to an excess of pulmonary tuberculosis and of anæmia. The relationship with tuberculosis, which was statistically significant, was true not only for the pregnancies studied but also for previous pregnancies. Anæmia (hæmoglobin value of less than 80%) was more frequent among mothers in all three groups with an abnormal outcome than among mothers of normal infants, significantly so in the group of stillbirths or neonatal deaths.

No infants with major defects were born to any of the few women in the series who had a specific infectious disease, but there was a statistically significant excess of acute febrile illnesses, mostly involving the respiratory tract, in mothers of infants with major defects.

There was also a suggestive relationship between acute illnesses, febrile and non-febrile, and both abortions and stillbirths.

No evidence was found that heavy work was related to abortion or stillbirth but a statistically significant excess of mothers of infants with major defects had been engaged in work which they described as heavy—particularly laundry work.

The raised incidence of infants with major defects among mothers with pulmonary tuberculosis, acute febrile infections and heavy work, I think deserves further study. It should not be difficult to determine the frequency with which women with pulmonary tuberculosis give birth to defective babies and not impossible to do the same for a large group of women engaged in heavy laundry work, but the problem of the minor febrile illnesses is less straightforward. Advantage might be taken of the fact that most women have blood taken in the third and fourth month for Wassermann and Rh tests and surplus serum might therefore be available for testing against various viral antigens.

## REFERENCES

McDONALD, A. D. (1958) *New Engl. J. Med.* (in press).
PATTEN, B. M. (1957) *Pediatrics, Springfield*, **19**, 734.

**Dr. R. G. Record** (Department of Social Medicine, University of Birmingham):

*Environmental Influences in the Ætiology of Congenital Malformations*

It has long been suspected that the pre-natal environment may have an important influence in the causation of congenital malformations and support for this view was provided by the discovery that maternal rubella in early pregnancy may lead to certain defects of the eye, ear and heart. Additional evidence from laboratory investigations has shown that in some animals malformations can be induced by feeding with vitamin-deficient diets, and by over-dosage with vitamins and by other means. It is not known what relevance these experiments have to the problem of human malformations and they do not seem to provide any explanation for the results of the few epidemiological studies that have been made.

There have been several attempts, mostly by retrospective enquiry, to relate human congenital malformations to disorders of pregnancy, but, except in the case of rubella, the evidence is scarcely convincing. There are serious objections to the retrospective method, and it may easily give rise to false conclusions unless suitable precautions are taken. The possibilities and limitations of the method can be illustrated by reference to the results of some investigations which have been carried out in Birmingham during the last ten years. In epidemiological studies of certain malformations, we enquired of the mother, some time after the birth, whether her pregnancy had been complicated by any disease or unusual event. The more important disorders considered are shown in Table I. Four of these

TABLE I.—PERCENTAGE FREQUENCY OF DISORDERS OF PREGNANCY AMONG MOTHERS OF DEFECTIVE CHILDREN

| | Excessive vomiting | Emotional shock | Falls and other accidents | Threatened abortion | Toxæmia | Rubella |
|---|---|---|---|---|---|---|
| Controls (742) .. .. | 5·0 | 0·3 | 0·0 | 1·1 | 5·1 | 0·0 |
| Anencephalus (305) .. .. | 9·2 | 1·3 | 1·3 | 3·6 | 4·9 | 0·0 |
| Spina bifida (309) .. .. | 6·5 | 1·3 | 1·3 | 1·9 | 3·9 | 0·0 |
| Pyloric stenosis (488) .. .. | 6·4 | 3·1 | 7·6 | 3·9 | 4·7 | 0·0 |
| Patent ductus arteriosus (150) | 4·7 | 4·7 | 6·0 | 4·0 | 7·3 | 2·0 |
| Congenital dislocation of the hip (167) .. .. .. | 9·0 | 0·6 | 4·8 | 3·0 | 7·2 | 0·0 |
| All malformations (1,419) .. | 7·2 | 2·2 | 4·3 | 3·3 | 5·1 | 0·2 |

No. of cases is given in brackets.

conditions (excessive vomiting, emotional shock, falls and accidents, and threatened abortion) appear to occur more frequently among mothers of malformed children than in the control group. There is some evidence, which cannot be given in detail, that the malformations considered here have very different ætiological features—anencephalus and spina bifida are laid down at an early stage of embryonic life; pyloric stenosis is dependent, at least in part, on factors in the post-natal environment; and some cases of patent ductus arteriosus and of congenital dislocation of the hip appear to be related to the conditions of birth. It would not be expected, therefore, that all these defects would be associated with

excessive vomiting in pregnancy, or with emotional shock, or falls, or threatened abortion. The fact that these episodes are recorded more often by mothers of malformed children is probably due to the mother's attempt to account for the defect, so that she recalls disorders of a trivial nature which the mother of a normal child would have no reason to remember.

This difficulty can be overcome by ignoring the control series and restricting the examination to a comparison between the different groups of malformations. Their diverse ætiology makes it unlikely that a disorder of pregnancy which was associated with one type would show a similar association with every kind of malformation. Mean frequencies based on the combined series of malformations are given in the bottom row of the table. For four disorders of pregnancy (excessive vomiting, emotional shock, threatened abortion, and toxæmia) the mean values are not exceeded by a significant amount by any of the malformations. The frequency of falls and accidents among mothers of children with pyloric stenosis appears to be significantly raised, but there are reasons for believing that this does not indicate a causal relationship. Histories of rubella were recorded only three times and all occurred in the patent ductus arteriosus group. Although the number is very small there is little doubt of a real association. But the great majority of cases of patent ductus appear to be due to some other factor. No other infectious disease has been recorded with sufficient frequency to suggest any causal relationship with any of the malformations studied.

It is concluded that very few of the malformations we have investigated can be accounted for by any remembered event in pregnancy. In attempting to explain this result we may consider the following possibilities:

(1) We may not have been asking the right questions, or we may have been disregarding information in the maternal history thought to be irrelevant, or the events in pregnancy of ætiological importance may be so trivial that they are not remembered. In these circumstances, a careful prospective enquiry should provide some information and we hope that we shall soon be able to report such a study.

(2) The second possibility is that human congenital malformations are determined entirely or almost entirely by inheritance and that environment plays little or no specific part in their causation. This seems to be unlikely for two reasons: it is very difficult to formulate acceptable hypotheses involving genes of full penetrance, and in most of the malformations we have studied we have found evidence of environmental influences. This evidence consists mainly of variations in incidence with the age and parity of the mother and with season, but more specific observations are available in the case of anencephalus, pyloric stenosis, patent ductus arteriosus, and congenital dislocation of the hip. Space does not permit a review of the evidence here: details may be found in the publications listed at the end of this paper. It is possible, of course, that variation of incidence with maternal age and parity and with season may reflect the action of environmental influences in removing malformed embryos from the uterus at an early stage of development. Nevertheless a review of all the evidence strongly suggests that the intrauterine environment plays some part in the ætiology of a number of congenital malformations.

(3) The most likely reason for our failure to relate most congenital malformations to events in pregnancy is that abnormalities in the intrauterine environment which cause malformations or are favourable to the continuation of development of defective embryos do not reveal themselves as overt maternal disease. It seems useless to speculate on the nature of these influences until more is known about the epidemiology of the various malformations.

## REFERENCES

*Anencephalus and Spina Bifida*

McKeown, T., and Record, R. G. (1951) *Lancet*, i, 192.

Record, R. G., and McKeown, T. (1949) *Brit. J. soc. Med.*, **3**, 183.

——, —— (1951) *Ann. Eugen., Lond.*, **15**, 285.

*Pyloric Stenosis*

McKeown, T., MacMahon, B., and Record, R. G. (1951) *Ann. Eugen. Lond.*, **16**, 249.

——, ——, —— (1951) *Lancet*, ii, 556.

——, ——, —— (1952) *Arch. dis. Childh.*, **27**, 386.

MacMahon, B., Record, R. G., and McKeown, T. (1951) *Brit. J. soc. Med.*, **5**, 185.

*Patent Ductus Arteriosus*

Record, R. G., and McKeown, T. (1953) *Brit. Heart. J.*, **15**, 376.

*Congenital Dislocation of the Hip*

Record, R. G., and Edwards, J. H. (1958) *Brit. J. prev. soc. Med.*, **12**, 8.

**Dr. J. A. McCredie Smith** (Manchester):

In the past thirty years there have been a number of studies of perinatal pneumonia, i.e. diagnosed histologically in stillbirths and in infants dying in the first week of life. Its significance as a cause of perinatal death has not been fully appreciated because the clinical features are elusive and the naked-eye findings at autopsy scanty.

When post-mortem examination of infants dying in the perinatal period is routine, and when the lungs of these infants are examined microscopically, the incidence of pneumonia is found to be considerable. Kjessler (1955) in 361 perinatal deaths found 70 with pneumonia. Ahvenainen (1953) noted that 206 (54%) of 384 infants who died during the first week of life had histological evidence of pneumonia.

We have carried out a study of pneumonia as a cause of death in perinates and an attempt has been made to determine some of the factors that contribute to infection of the fœtus. The study is in two parts—a retrospective investigation which consists of contrasting the infants with pneumonia against those who showed no evidence of pneumonia. The second part is a clinical investigation into the exact part which infection played in causing perinatal death. This investigation was necessary because many workers have observed that the lesions found post mortem in stillbirths and in infants dying shortly after birth are usually multiple, and it is often difficult to determine which lesion is the principal cause of death and which contributory. So, the presence of pneumonia, which is the commonest evidence of infection, does not necessarily represent the significance of infection as a cause of death.

*Retrospective Study*

This comprised 90 perinatal deaths seen in the years 1950, 1952 and 1954. About 10% of stillborn infants showed evidence of pneumonia but pneumonia occurred in 25% of infants dying on the first day of life and in 30% of those dying on the second day. Thereafter it became of relatively less importance. Though pneumonia was more common in non-macerated stillborn infants, it frequently occurred in macerated infants. This indicates that infection is not just a terminal event but can sometimes occur before birth.

It is obvious then that assessment of the role played by pneumonia in causing death is very difficult.

Because this was a retrospective study much of the information that was required was not recorded on the notes. The only significant maternal finding was that prolonged rupture of the membranes (over forty-eight hours) occurred more frequently in the pneumonia series as compared with the control series.

The next factor to be examined was the placenta. Inflammation of the placenta can occur at several sites. Initial studies indicated that inflammation of the chorion or round the vessels of the fœtal surface was important. There was a highly significant correlation between inflammation of the fœtal surface of the placenta and the occurrence of pneumonia, and at the same time the fœtal vessels were frequently involved. These findings suggest that not only can a fœtus be infected by aspiration of infected liquor but that infection spreading via the blood stream is also very important.

*Prospective Study*

As our experience suggested that infection plays a considerable part in the causation of perinatal mortality and morbidity, an investigation was designed to determine the significance of infection as a cause of death.

Two groups of women who were either in labour or whose membranes had ruptured were selected from those admitted to hospital. The first group were all those thought to have an intrapartum infection, 137 in total. This group was further divided by strict alternation into 68 patients treated with antibiotics and 69 who received no antibiotics. The second group was a control group in whom no intrapartum infection was suspected. This consisted of every fifth patient admitted in labour into the hospital and numbered 99 in all. There are obvious shortcomings in the control group.

The diagnosis of intrapartum infection was based on two criteria: a maternal pyrexia of 98·6° F. or over, measured on a four-hourly temperature chart, or a fœtal tachycardia of 160 or over, maintained for ten minutes. The presence of either of these criteria was taken to indicate intrapartum infection. A full bacteriological and pathological examination was made in all cases.

For the purpose of the therapeutic trial alternate women admitted into the infected group were given combined antibiotics—intramuscular streptomycin 1 gram twice daily and oral oxytetracycline 500 mg. six-hourly—from the time the infection was diagnosed until the patient was delivered. A combination of two antibiotics was used because the organisms were unidentified on admission to the trial, and because the organisms were less likely to develop resistance.

*Results*

The treated and untreated infected groups were alike with respect to the relative frequency of maternal pyrexia and fœtal tachycardia, and in age, parity, social class and in the frequency of toxæmia, surgical interference and prolonged labour. However, they differed from each other, and from the uninfected control group, in their incidence of notifiable puerperal pyrexia and in perinatal mortality (Table I).

| Group | Total patients | Puerperal pyrexia | Fœtal deaths Total | Fœtal deaths With evidence of pneumonia |
|---|---|---|---|---|
| Infected—not treated.. | 68 | 18 (26%) | 10 (15%) | 5 |
| ,, —treated .. | 69 | 9 (13%) | 5 (7%) | 0 |
| Not infected (control) | 99 | 5 (5%) | 0 (—) | 0 |

Notifiable puerperal pyrexia was commonest in the infected untreated group, 18 cases out of 68, a morbidity rate of 26%. The treated group had half that rate, 9 cases out of 69, 13%, and the uninfected group least of all, 5 cases out of 99, 5%. The difference between the infected untreated group and the uninfected group was most unlikely to be fortuitous.

Fœtal death was commonest in the untreated infected group, 10 deaths out of 68 (fatality rate of 15%) of which 5 gave evidence of pneumonia. Among the 69 treated infected patients there were only 5 deaths (fatality rate of 7·2%), none with evidence of pneumonia. In the 99 uninfected controls there were no fœtal deaths at all. Most of the deaths, including all the pneumonias, in the infected untreated group were of infants whose mothers had over forty-eight hours infection, measured from the first sign until delivery. The difference in fatality rate between the infected untreated and the uninfected controls was highly significant, but the difference between the treated and untreated groups of infected patients was not formally significant ($p > 0{\cdot}05$) except among those with over forty-eight hours' duration of infection.

The pathogenic organisms associated with perinatal deaths were mainly *Escherichia coli*, *Streptococcus fæcalis*, non-hæmolytic streptococci, and rarely a hæmolytic streptococcus. 38% of presumed uninfected women had pathogenic organisms in the upper vagina, but only 2% of placental blood cultures were positive. In the untreated infected group the corresponding percentages were 73%, with 13% of positive placental blood cultures. Furthermore in certain instances in which there was a fatal pneumonia in the infants the vaginal swab, the placental blood, and the lung culture all showed the same organisms.

The mechanism of fœtal infection may be explained as follows: Bacteria commonly found in the vagina, or introduced by the attendant, enter the uterus and infect the decidua. In some women, infection spreads to the placenta or membranes or both. Often the infection gets no farther, but sometimes it spreads to the fœtus by the fœtal blood stream or by aspiration of infected liquor. The effect of perinatal infection is usually relatively slight on the mother but can be disastrous for the infant, because organisms of relatively low virulence for the mother have a much greater effect on the infant, who has little or no immunity. Such a concept is consistent with the higher frequency of puerperal pyrexia in infected cases than in controls.

The bacteriological studies of the vaginal flora suggest that antibiotic therapy reduces the incidence of potential pathogens. The effect on the fœtus may therefore be twofold: antibiotic therapy may eliminate some or even all of the organisms in the vagina so that infection of the fœtus is prevented; or, if the infection is established in the fœtus, it may control it and facilitate recovery. Furthermore, the combination of antibiotics used in this investigation tends to reduce the possible development of resistant strains of organisms.

## REFERENCES

AHVENAINEN, E. K. (1953) *Ann. Med. intern. Fenn.*, **42**, suppl. No. 17.
KJESSLER, A. (1955) *Acta obstet. gynec. scand.*, **34**, suppl. 1.

# Section of Anæsthetics

President—B. L. S. MURTAGH, M.B., F.F.A.R.C.S.

[*January* 3, 1958]

## DISCUSSION ON ORGANIZATION FOR IMMEDIATE POST-OPERATIVE RECOVERY PERIOD

**Dr. Russell M. Davies** (East Grinstead):

A patient leaves the operating theatre with three handicaps to his return to health.

(1) The basic pathology, namely the disease process.
(2) The blood loss and trauma of surgery.
(3) The residuum of anæsthesia.

It is at this time that the need for skilled and continuous care is greatest. This period may be short or long. The after-care needed may be complicated, requiring the intervention of many medical specialists; or it may be simple. Whichever it may be, vigilant nursing will always be required for the appropriate period. In seeking this degree of care it is difficult to concentrate all the required skills in the right place at the right time. Where several such patients are scattered around the hospital dispersal will be wasteful of both doctors and nurses. This will always be true whatever the size of the hospital. Where the hospital is anything but a small one, surely it is logical to have a single place where all these desirable skills may be applied to the patient, and I would submit that the best place would be a recovery ward.

The provision of such a focal point is becoming more and more urgent. Skilled nurses are increasingly difficult to obtain. This difficulty will be felt first, and in fact is already being felt, in the peripheral non-teaching hospital; but in time it is probable that it will be felt too in the teaching hospital and this shortage of trained nurses was one of the most potent factors in the U.S.A. in spreading the institution of the recovery ward. In 1954 a questionnaire was sent out by the American Hospitals Association (Higgins, 1954) asking the hospitals whether they had recovery ward facilities of any sort and the following are some of the figures which were obtained. Of the smaller hospitals, 2% had recovery ward facilities; of the medium sized hospitals, 42% had recovery wards; of the largest hospitals, 55% had recovery ward facilities. The totals showed that out of 3,000 hospitals answering the questionnaire, 1,300 had recovery wards of one sort or another and the bigger the hospital the more likely was it to have a recovery ward. Since 1954 it is almost certain that these numbers have been increased. In this country, too, I am sure we will see the increasing adoption of the recovery ward as the best means of using the nursing skills which will be decreasingly available to us.

The recovery ward may be nothing more than a simple single room for the accommodation of selected patients as they leave the operating theatre, or it may be a large open space fitted with oxygen and suction. Alternatively it may be a large many-roomed unit or it may combine both arrangements, with a relatively large area in which the truly transient patient may be nursed, together with individual rooms to accommodate the seriously ill and longer stay patient. I think it is fair to say that there is no one ideal plan for a recovery ward, which must be designed to serve the surgical and geographical needs of the hospital so that it will be able to nurse the greatest possible number of patients. Where the hospital is a scattered unit the ward may be a large one, where the hospital is a compact unit the recovery ward may be a smaller one; but whatever the design I feel that certain principles must be observed in establishing such a ward. In February 1946 a recovery ward of 10 rooms was opened at the Queen Victoria Hospital, East Grinstead. During this period of slightly under twelve years, the ward has nursed approximately 33,000 patients, and out of this experience the following principles have come.

(1) *The ward should be staffed for twenty-four hours a day.* It is in fact easier, administratively, to staff a ward round the clock than to open it from 8 a.m. to 8 p.m. Furthermore, twenty-four-hour staffing will mean that the ward is always available for those who frequently need it most—the surgical emergencies. In the case of our own ward, normal ward staffing arrangements are followed throughout the day and night. There is a charge-nurse supervising the ward with the rank and pay of a departmental sister. The nursing administration comes directly under the Matron of the hospital and not under any other departmental sister. The sole duty of the nursing staff is to care for the patient in the post-operative period and thus develop interests and skills more single-mindedly than if their appointment was a joint one to one or two units in the hospital.

(2) *All patients who have had general anæsthesia should pass through the ward.* Any other procedure involves guessing which patients will give trouble in the post-operative period and which will not. Inevitably, one day, one will guess wrongly, maybe with a fatal result.

(3) *The standard of nursing skill in the ward must be equal to the best in the hospital.* Some nurses make better theatre nurses than others, and some better surgical ward sisters than others. Similarly there is no question but that some nurses make better recovery ward nurses than others. The good recovery ward nurse is no more skilled than any other able nurse. It just happens that her aptitude is different. This skill must be sought for and employed. Above all, such a nurse must have the ability to observe a patient from moment to moment and act unerringly, frequently at speed, upon the results of these observations.

(4) *The nursing staff should never be moved from the ward as a group.* Nursing training is most easily and effectively carried out at the bedside. It is necessary to have in the ward not only a constant level of ability and knowledge, but also a continuous informal training programme. This can best be done by making single staff changes rather than block changes so that an even level of knowledge and skill is maintained in the ward. Furthermore an attempt should be made to retain at least one of the staff for a prolonged period at least of months to act as an efficient deputy for the ward sister when she is off-duty. At the present time at the Queen Victoria Hospital, East Grinstead, for our recovery ward of 10 rooms the staff is as follows: By day—one male nurse in charge with the status of a sister, four State-registered staff nurses who are moved from the ward at intervals varying from one year down to six weeks, and, finally, two ward orderlies. At night the staff consists of one State-registered nurse and one nursing aid. Whenever the number of night emergencies admitted to the ward rises, it is accepted by the nursing administration of the hospital that this number of night staff should be augmented, even at the expense of depleting the night staff elsewhere in the hospital.

(5) *The level of record keeping must be high and all ward procedures must be adhered to as rigorously as in other wards.* Record keeping must be accurate and detailed because it must be realized that the introduction of a recovery ward forges another link in the chain of patient care. Information must be received and understood when the patient arrives from the operating theatre. This, with the addition of the recovery ward information, must be accurately transmitted when the patient returns to his own ward. This link must be unbreakable. The records will be of two types: firstly, those maintained for ward purposes—including details of the reception and discharge of the patient, treatment records, drug records, &c.; and secondly, the patient's records. These will include all details of the surgical procedure, post-operative incidents, or the lack of them, and all treatment while the patient is in the recovery ward, and these must go with the patient to his own ward. We have found that this is most readily done by the sister making the appropriate entries as an integral part of the patient's case notes. These must be completed before the patient leaves the recovery ward for his own ward.

(6) *The recovery ward must be close to the operating theatre.* It has been our practice that the sister of the recovery ward or her deputy goes to the operating theatre to receive the patient from the surgeon and anæsthetist. The patient is placed in the recovery ward bed at the operating table side and at the same time instructions are given on the immediate post-operative care required. When the ward is close to the operating theatre it is also possible for the surgeon and anæsthetist to make frequent visits to see their patient, and indeed it soon becomes a habit to do so. Finally, the distance which the patient will have to travel will be a short one, and the report by Pask (1955) emphasizes the importance of this point.

(7) *The recovery ward must be adequately equipped with resuscitative equipment.* Piped suction and oxygen are at the very least a convenience. All the necessary solutions for infusion should be readily available.

(8) *Medical care must be immediately available in the ward at all times.* It has been our practice to regard the senior house officer in anæsthetics as having the same relationship to the recovery ward as has the house physician or house surgeon to *his* wards. It is his responsibility to call the appropriate consultant in the event of any crisis arising. He will visit the ward from time to time during the day and also before going to bed at night. When he is off-duty alternative cover is provided by the other junior staff. In addition, at all times throughout the day and night a senior member of the anæsthetic staff is available for consultation and call. Finally, the nursing staff must be kept aware of the whereabouts of the doctors to whom reference may be made.

(9) *There should be facilities for the retention of a patient in the recovery ward for as long as the facilities of the ward will benefit the patient.* In our experience the stay of the patient in the ward has varied from 20 minutes to 13 days. 95% of the patients stay in the ward twenty-four hours or less, but again the practice will obviously vary both with the methods adopted in different hospitals and also with the type of surgery that is done. For example, in the Research and Educational Hospital of the University of Illinois in Chicago, 10% of all patients stay in the recovery ward for forty-eight hours or more. On the other hand in St. Mary's Hospital, Rochester, Minnesota, the recovery ward (or Post-Anesthesia Room, as it is called) is open only from 8 a.m. to 5 p.m. (Mayo Clinic Section of Anesthesiology, 1945), no patients being admitted after the latter hour.

## Discussion

Publications from this country and America leave no doubt of the life-saving function of the recovery ward. At different times articles have appeared analysing the post-operative care of something like 100,000 patients, and in all instances the opinion has been given that as a result of the institution of these wards lives were saved. In re-reading Pask's article of 1955 one cannot but feel that many of the deaths which he recorded would not have happened had adequate and readily available nursing care been at hand. He gives the opinion that death in 58 cases appeared to be due to an insufficiency of post-operative care. He says "in 49 the fatal process began as a respiratory disturbance—either obstructed respiration or inadequate respiratory movements; in 20 cases the patient was found dead, and in 8 of those the patient was found dead on arrival in the ward from the operating room, and in 7 the journey was a long one; in 10 cases the inhalation of vomitus or blood could clearly be identified as the critical event; there were 19 cases following the use of a relaxant, when respiratory insufficiency (other than obstruction) was present post-operatively and again the attendant was an inexperienced one". Our own experiences would confirm all these impressions.

Among the 33,000 patients for whom we have cared following surgery there have been many anxious moments. These moments have occurred often enough for us to feel that any attempt to prophesy which patient would encounter post-operative difficulties is fruitless. Of this number of patients a total of 11 have died, and of these 11 we believe that *one* would be classed as avoidable by the investigators of the Association of Anæsthetists. This gives an overall mortality rate of approximately 1/3,000, compared with a rate of 1/1,300 before the ward was opened.

Finally, a recovery ward has two advantages and one disadvantage. It saves lives and it saves nurses; but it costs money.

## References

Higgins, H. G. (1954) Personal communication.
Pask, E. A. (1955) *Anæsthesia*, **10**, 4.
Mayo Clinic Section of Anesthesiology (1945) *Proc. Mayo Clin.*, **20**, 292.

**Mr. J. R. Belcher** (London):

The immediate post-operative recovery period should cover at least forty-eight hours. By no means all the emergencies occur within the first six hours and the small hours of the morning appear to be particularly dangerous.

Secondly it is essential that there should be some sort of transition stage between the end of an operation and the return of a patient to an ordinary ward. Clearly the details of this transition must vary widely from hospital to hospital, for both the type of work and the topography must have a dominant influence upon the arrangements.

These opinions have been confirmed by my experience at the London Chest Hospital, where we have what I consider to be an almost ideal recovery ward arrangement. However, relatively few very major cases are operated upon each week, in contrast to the situation at East Grinstead.

Some of the arguments in favour of the "recovery ward" principle are as follows. It is possible to concentrate an adequate number of experienced and competent staff there: it is possible to have readily available all the apparatus which may be required in an emergency: bronchoscopes, suckers, transfusion sets, mechanical respirators, equipment for cardiac resuscitation, &c., and lastly nocturnal disturbance of convalescent patients can be avoided by this segregation.

I do not agree with Dr. Davies that all patients should pass through such a ward, but that only major and complicated cases should do so. This is not, in fact, a view widely divergent from his, for I believe that no patient should leave the theatre suite until he is "round" and breathing satisfactorily. The corridor outside the theatre may well thus be regarded as a primitive form of "recovery ward". I also believe that patients who have been "cooled" should not leave the theatre, let alone the suite, until their temperature has reached at least 35° C. and until they are showing signs of spontaneous respiration. The anæsthetist's attention should not be divided at this stage.

I believe that a recovery ward must have a whole-time staff and that the "nine till five" system may be dangerous. At the London Chest Hospital the patients are transferred to the ward before their operation and kept there for at least forty-eight hours after it. We find that eight beds are sufficient to cope with our average weekly list of 10 cases.

Ideally the ward must be near the theatre, and on the same floor. It can thus be easily accessible should anything go wrong in the middle of a list. It must be well lit, but fluorescent lighting should be avoided as it makes cyanosis difficult to recognize.

I shall now go on to define the hazards which a recovery ward is designed to lessen.

Perhaps the commonest cause for alarm is respiratory obstruction. This may be due to a variety of causes, most of which are easily corrected, but should they occur in the hands of an inexperienced nurse during the transit between a theatre and a distant ward they may be lethal. The second hazard is anoxia which may also be due to a variety of causes, such as respiratory depression and blocked tubes. Again these may be easily dealt with in a well-equipped ward, but not in a lift. The same comments apply to the third hazard—carbon dioxide retention. Major hæmorrhage is the fourth catastrophe which has to be prepared for. The time saved in a ward where blood and apparatus are readily available may be life-saving. Lastly, cardiac arrest: this is happily uncommon in Britain. Nevertheless it does occur, but as it is almost always fundamentally due to anoxia, it is my conviction that it may often be avoided by timely bronchoscopy in those patients whose major bronchi have become obstructed by blood or vomit.

Should arrest occur, thoracotomy and massage must be rapidly undertaken. The procedure is easy, but the decision to open the chest is difficult; for this reason it is not often successful. It is certain, however, that apparatus and, more important, trained staff should be immediately available: hence the necessity of a recovery ward near the theatre.

These are some of the disasters which have to be provided for. My last point is concerned with who should be responsible for the treatment of these complications when they occur. There is a considerable risk of over-treatment of patients at this stage, and one man should therefore have overall responsibility. Most of the hazards are to a greater or less extent related to the anæsthesia, and the anæsthetist should be reponsible for their treatment. As a corollary, I think that all anæsthetists should have some of their training in a chest unit where bronchoscopy is common and cardiac arrest by no means unknown. In a general hospital it is clearly impossible for all the surgical registrars and house officers to become familiar with the techniques which may be required in an emergency, and therefore I think that the limited experience available should be acquired by one man: the senior resident anæsthetist.

**Dr. T. B. Boulton** mentioned that a report on the working of their post-operative observation ward at Southend-on-Sea was published by Jolly and Lee in January 1957 (*Anæsthesia*, **12**, 49). All concerned were now agreed that the benefits of having a post-operative observation ward far outweighed the disadvantages, and that this was especially true in any hospital where there was a shortage of nursing staff.

The danger of the recovery room becoming a kind of medical "No Man's Land" was a real one, but this had been overcome by careful co-operation between surgeon, anæsthetist, and physician. It was certainly essential that a single registrar should have responsibility for the post-operative observation ward. Like Dr. Davies, they had found that this duty was most easily performed by the senior of the anæsthetic registrars.

Three distinct types of case passed through their recovery room:

Firstly: Trolley cases, relatively minor surgical procedures on fit individuals who remain only for a short while to recover completely from their anæsthetic.

Secondly: More major surgical procedures who remain in their beds for twelve to twenty-four hours before being returned to the wards.

Thirdly: Very ill patients who require special nursing for several days.

Perhaps the last group did not strictly belong to the province of the post-operative ward, but the fact that surgeons often preferred to leave such patients in the ward bore ample testimony to the quality of the specialized nursing skill available.

During a recent visit to the United States where the nursing shortage is acute, it was certainly evident that the recovery ward had become an essential part of the surgical set-up. In some centres, such as in the hospitals associated with the Mayo Clinic, specialized techniques such as hypothermia and cardiopulmonary by-pass had caused the development of specialized long-term recovery units. As cardiac operations became more complicated and radical, it might even be necessary to provide sleeping accommodation in the Unit for the use of medical staff so that they might be close at hand during the early post-operative period.

Besides the benefits of close supervision of post-operative patients, the post-operative observation ward brought facilities for simple clinical research within the reach of the ordinary working anæsthetist. Ward sisters and nurses in general wards could not be expected to help in observing and recording special data, but in the post-operative ward they could and did help; indeed recording such data should be part of the routine.

They did not agree with Mr. Belcher that it was a good thing for patients to be admitted to the post-operative ward prior to operation. One individual, who was sometimes forgotten when considering the pros and cons of recovery rooms, was the patient low on the operating list who, but for the recovery room, was forced to see his fellow patient returning from the theatre festooned with all the paraphernalia of modern surgery—drips, drains and the like. Occasionally, even in these days, the patient vomited or was shocked or delirious. How much better that the pre-operative patient should be spared the mental trauma of seeing his ward-mates in the early post-operative period.

With the modern methods of rapid induction at their disposal, one might almost say that a post-operative recovery ward was more essential than a pre-operative anæsthetic room.

**Dr. A. C. Fraser** said that there had been a recovery room at Lincoln County Hospital for five years. It was adjacent to the theatres, worked from 9 a.m. to 5 p.m. and patients stayed about an hour. Eight beds were sufficient for two busy theatres. They had always managed to find a part-time sister to staff the room and the theatre provided extra help when needed. To make up for some loss of experience groups of student nurses came to the theatre for special instruction in post-operative care and an anæsthetic nurse was appointed each month to help the anæsthetists.

**Dr. Eric Gardner** pointed out that a fully equipped recovery room with its specially trained staff under the anæsthetist's supervision was the ideal place for the treatment of certain medical emergencies, such as barbiturate poisoning, tetanus and other cases of respiratory failure.

**Dr. G. F. Rawdon Smith** thought that one of the main difficulties in the provision of such a ward was the shortage of hospital beds throughout the country and that the use of one ward for both pre- and post-operative cases had practical objections. He was also afraid of still another specialty being created in an already over-burdened profession.

**Dr. J. Alfred Lee** felt that the success of a post-operative observation ward depended largely on the efficiency and devotion to duty of the nursing staff. He made the suggestion that the name of such units should be Post-operative Observation Wards. The unit was primarily for careful observation and as such it fulfilled a most useful function.

**Dr. Laurence Mountford** said that while it was true that most cases of cardiac arrest were anoxic in origin, and bronchoscopy might well remove the cause of anoxia, bronchoscopy in itself could readily be a cause of cardiac arrest, especially in the presence of poor respiration, when suction would reduce the alveolar oxygen to disastrous levels. Bronchoscopy could be safely carried out only in the presence of two conditions: full respiration and a blood pressure within near-normal limits.

If patients were returned to the ward in an adequate state of recovery, the physiotherapist could immediately begin the treatment designed to prevent atelectasis, a very important part of post-operative recovery.

If the responsibility for post-operative care was to lie with the S.H.O. in anæsthetics, then it was most important that the R.S.O. should have continuous access to his patient in order not to miss a most vital part of his training.

**Mr. St. John Birt** said that, as a surgeon concerned in planning a new theatre block for a small provincial hospital, he was particularly interested in the number of beds which should be made available in a recovery room in relation to the amount of operating carried out in the theatre, and that as both the opening speakers came from large centres doing specialist work, it would be helpful to have the views of those carrying out more general work.

As to whether the surgeons or the anæsthetists should be in immediate control of post-operative recovery, he felt that surgeons were now in the same position in relation to the treatment of shock as they had been in relation to the giving of anæsthetics twenty years ago. At that time the surgeon felt responsible for the anæsthetic and was not averse to giving advice as to how it was to be administered. To-day he would not consider tendering such advice. However, he still gave advice about the treatment of shock, but as in most cases anæsthetists knew a great deal more about this treatment than surgeons, Mr. Birt considered it was time that the surgeon handed over the treatment of the patient's general condition in the immediate post-operative period to the anæsthetist.

**Professor E. A. Pask** asked whether patients whose operations were associated with special metabolic problems (e.g. hypophysectomy) should be taken to recovery wards or should return immediately to the care of the specialist teams. He wondered also whether a patient who had been ill for a long time and deeply trusted the nurses who cared for him, might not be distressed to recover consciousness amongst strangers.

Professor Pask spoke of experience in a hospital with widely separated single operating-rooms, not always very logically arranged in relation to their wards. In these circumstances, although a central recovery ward would be economical of nursing staff, many of the post-operative patients would be far from the surgeons and anæsthetists.

**Mr. Belcher** in reply also stressed that the recovery ward should be as near to the theatre as possible, and that no standard plan is possible as hospitals differ so much in their lay-out and in the type of work carried out.

**Dr. Davies** in reply to Professor Pask gave as his opinion that where the choice lay between concentration of recovery ward facilities and proximity to the operating theatres, the latter would be the choice which he would support. [Mr. J. R. Belcher later agreed with this view.] In Dr. Davies' opinion even where patients have gained confidence in and come to depend upon their ward staff, provided that the ideas behind the recovery ward were explained before operation, they appreciated the period of quietude and seclusion in the specialized surroundings of the recovery ward in the immediate post-operative period.

With regard to such cases as hypophysectomy, he felt that each unit would no doubt make arrangements best suited to local circumstances, but he felt that the facilities of the recovery ward should not be completely disregarded.

In reply to questions concerning the ratio of recovery ward beds to operating theatres he mentioned several methods of calculation which had been suggested in the past. (*a*) Two beds per operating table. (*b*) A number of beds equal to the maximum possible operating list. (*c*) A number of beds equal to the average number of cases per day.

At East Grinstead the latter scheme had been adopted, and they had found that ten beds could handle 3,000 cases a year satisfactorily, but they were somewhat cramped when the number rose to 3,600.

In reply to a further question Dr. Davies stated that the House Surgeon to any case was urged to visit his cases in the recovery ward as often as he wished, in order to give the appropriate post-operative surgical care. There was not, and could not be, any sense of competition between surgical and anæsthetic departments in this ward. The work of the two was complementary, and resulted in no loss to the post-graduate training of the surgeon.

Finally, in reply to Dr. J. Alfred Lee, Dr. Davies pleaded that the name," recovery ward", should be retained in spite of alternative suggestions which have been made from time to time. It was a term which was easily understood, together with its implications, by the patient.

*Proceedings of the Royal Society of Medicine*

Vol. 51
157

# Section of Neurology

President—W. RITCHIE RUSSELL, C.B.E., M.D., D.Sc., F.R.C.P.

[*December* 5, 1957]

## The Ætiology of Polyneuritis

By A. M. G. CAMPBELL, D.M., F.R.C.P.

*Bristol*

I PROPOSE to consider only the ætiology of so-called infective polyneuritis or the Landry-Guillain-Barré syndrome.

Since the paper of Haymaker and Kernohan (1949) it has generally been accepted that the cases described by Landry (1859) and those by Guillain *et al.* (1916) are the same, the only difference being that Landry emphasized a brief, rapidly spreading, ascending paralysis with minimum sensory disturbance, whilst Guillain emphasized particularly a rise in the protein of the cerebrospinal fluid as being characteristic of this disorder. It is probable that most of Landry's cases were similar to those of Guillain but he was unable to examine their spinal fluids.

On the other hand it is undoubtedly true that some of Landry's cases may not have been similar and as Symonds (1949) has pointed out there are cases resembling those described by Landry which may arise from a biochemical lesion which has been unsuspected and may, as Symonds stated in this paper, be due to potassium poisoning and secondary to uræmia and renal disease. These, however, must be rare and the majority of cases are probably infective polyneuritis. Haymaker and Kernohan (1949) also drew attention to the fact that the protein in the cerebrospinal fluid is not always raised at the start of the illness but rises to a peak over the ensuing months and only begins to fall when the paralysis starts to improve. He also emphasized in his large series of cases that about 10% have a small cellular rise in the spinal fluid and not all cases show complete absence of cells.

Recent work has tended to emphasize that the Landry-Guillain-Barré syndrome is a non-specific reaction to several infective agents and is due possibly to an abnormal antigen-antibody response. Miller (1955) has also claimed that it follows specific fevers such as measles, but Tyler (1957) (in a recent review of the neurological complications of measles in the United States) has denied this and found no case of infective polyneuritis associated with measles, nor in any of the cases that I have seen has any specific fever preceded the polyneuritis.

What has been striking in examining the literature is what Haymaker and Kernohan (1949) suggested, that sometimes there is an association with an illness resembling glandular fever before the onset of the polyneuritis and that some of the cases at least show a lymphocytosis before the onset of the illness. The second point which emerges very clearly from examining my own cases and the literature is that in about 60% of cases there is a respiratory infection with cough, sore throat and pyrexia before the onset of the polyneuritis and in another 10% to 20% of cases the onset is heralded by an attack of diarrhœa. It is interesting to compare this with the onset of poliomyelitis which also can be preceded by a respiratory infection and sore throat or an enteric infection. In Haymaker's series two cases followed injections of anti-tetanic serum. Again there is some resemblance to poliomyelitis in the precipitation of this disease by an injection.

This condition does not resemble the allergic encephalomyelitis following specific fevers such as measles and chickenpox, but does, in point of fact, resemble what previous workers have suggested, a virus infection of unknown ætiology and there is some evidence from previous experimental work that this in fact may be so.

Many writers have expressed the opinion that human cases of infective polyneuritis were due to a virus infection. Leschke (1914) injected material from the spinal cord of a case of ascending paralysis in a 16-year-old girl into a monkey by both intracerebral and intraperitoneal routes and on the ninth day the monkey became paralysed and died.

Negative experiments were carried out by Lassen *et al.* (1943) who did not use monkeys but chiefly mice, rabbits and ferrets. Sabin and Aring (1941) also failed to convey the disease to mice, guinea-pigs and on one occasion a monkey. The most important work in this field, so far, has been that of Pappenheimer *et al.* (1951). They sent the fæces of a child

aged 4 years with progressive motor paralysis, to test for the virus of poliomyelitis by injecting material into monkeys. This produced lesions which were not those of poliomyelitis but severe degenerative inflammatory lesions of the spinal roots closely resembling the Landry-Guillain-Barré syndrome. They injected six monkeys intracerebrally and at post-mortem three of these animals showed neuronal degeneration of the spinal roots and peripheral nerves with or without marked lymphocytic infiltration. Further passage carried out by injection of spinal cord suspension of these animals was followed by the development of similar lesions in two of the six animals injected. Thus, five monkeys showed positive symptoms and pathological changes similar to infective polyneuritis, and in two others minor changes were found.

An attempt to transmit the disease to mice failed. Nor could further passage be established and no definite virus was isolated, but the experiment is of considerable importance as it was carried out with very strict control and in the second experiment material was kept for two years and this coupled with antibiotics was injected into the second group of monkeys thus excluding the possibility of an accidental virus infection of the monkeys themselves.

Many of the experiments that have failed to transmit this disease, may have failed because the virus was only pathogenic to monkeys and not to ferrets, mice, guinea-pigs and smaller animals which have been used. A search through the literature fails to reveal that any attempt to transmit the infection to a cat has ever been made.

The present investigation arose as a result of the speaker seeing a case of this disease three and a half years ago in which the story was that the patient's cat became ill with a respiratory infection called "cat influenza". Within a few days the patient's wife caught an influenza-like illness and two days later the patient became ill with a similar illness with respiratory symptoms followed within seven days by the onset of severe motor paralysis. This patient had a prolonged illness of the Landry-Guillain-Barré type, his proteins reaching 400 mg.% and is still left with some residual paralysis, the whole illness taking approximately nine months. His cat recovered and is still living.

Since seeing this patient 5 other personal cases have been seen in which the onset of the disease was directly related to an illness of the patient's cat. In one case the cat died and the diagnosis made by the veterinary surgeon was feline enteritis. In another case the cat had been diagnosed as cat influenza and in the other three cases the cat had had no veterinary attention and had recovered spontaneously after about two weeks' illness. When questioned, the patients were somewhat uncertain about the symptoms shown by the cat, but in two cases there was definite diarrhœa.

An analysis of all the cases of infective polyneuritis seen by myself in the last three years showed that in all there were 12 cases which all satisfied the criteria on clinical grounds. All had raised protein in the cerebrospinal fluid. Out of these 12 cases, 2 died, 1 on the first day of the illness of respiratory failure and 1 during the period of recovery, after having been in an iron lung, had a sudden pulmonary embolism and died on the twenty-first day of the illness.

10 cases have started with a respiratory illness with cough, sore throat and influenza-like symptoms. 2 started with diarrhœa which preceded the polyneuritis by one week and three days respectively. 5 cases had not had contact with a sick animal but had cats in the house at the time of the onset of the illness and one man, the patient who died after twenty-four hours' illness, had the cat to sleep with him in his bed, although it must be admitted that the cat had not apparently had any symptoms of illness.

These results were sufficiently striking to inquire whether other people have had similar experience. Dr. T. G. Reah of Harrogate reported a similar case who developed an infective polyneuritis about a month after her kitten had had what was probably feline enteritis. She herself attributed the illness, oddly enough, to contact with this sick cat which she had nursed throughout its illness. The more interesting letter was received from Dorset about 2 patients of Dr. E. B. Jarrett's. The first was a farm worker aged 48 who developed a picture resembling very closely that of infective polyneuritis and was admitted to hospital in Dorchester where he made an uneventful recovery. It must be added that although he had had syphilis in the past and had a positive Wassermann reaction in his cerebrospinal fluid and blood, Dr. Jarrett was of the opinion that the picture was not that of neurosyphilis but a genuine polyneuritis and there were no cells in his cerebrospinal fluid, his protein being well over 300 mg.%. This patient's cat was sent to a lady forty miles away to be looked after while its owner was ill. After a month it sickened and died of feline enteritis and this lady aged 65, a school teacher, was admitted with an acute infective polyneuritis and an attack of diarrhœa from which she died. She had progressive weakness of all limbs of very rapid onset and after being placed in a respirator she died ten days after the first symptoms. Cerebrospinal protein examination was carried out and was 160 mg.%; cells were 3.

If, as is probable, these were both cases of infective polyneuritis there was this very interesting story of a link between these two cases of a somewhat rare disease by the same

cat which eventually died from what the veterinary surgeon considers to be definite feline enteritis.

Subsequent to this, I have heard of 2 other cases linked with an illness in a cat.

On clinical grounds, therefore, there appears to be quite strong evidence, which is difficult to imagine as pure coincidence, that this syndrome can at least occasionally be linked with an illness of cats.

The help of Messrs. Burroughs Wellcome was enlisted to investigate this problem and I must pay tribute to the help I have received from Mr. A. B. MacIntyre at their Veterinary Research Laboratories.

There are two main infectious diseases of cats, the first is an influenza-like illness infecting the lungs and is due to a large virus of the same family as that which gives rise to psittacosis and lymphogranuloma inguinale. After consultation with Mr. MacIntyre and after negative Frei tests on our patients he considered that the evidence that this was the disease responsible was not great and he thought it far more likely that a much more serious infective condition of cats, feline enteritis, might be responsible for the illness in the cats and human beings and it is on this assumption that work has proceeded.

Feline enteritis in cats has a mortality of about 20% and is highly infectious from animal to animal, chiefly affecting young cats and kittens, and probably 70% of all cats at some time or another are infected. The disease is characterized in cats by a general inflammatory reaction of the gut, intense diarrhœa, agranulocytosis and enlargement of the lymph glands.

Messrs. Burroughs Wellcome have developed a vaccine against this virus which has helped to control this infection.

They have carried out complement-fixation reactions on the serum of my patients who have suffered from infective polyneuritis, using as antigen cats' tissue (spleen and lung) infected with feline enteritis virus and also two tissue cultures similarly infected. Using a limited number of laboratory workers as controls the results, as far as they have gone, have suggested that there is a distinct difference between the patients' bloods and those of the controls and suggest that it may be possible to get pathological confirmation of the clinical association of infective polyneuritis with cats.

## REFERENCES


BRADFORD, J. R., BASHFORD, E. F., and WILSON, J. A. (1918) *Quart. J. Med.*, **12,** 88.

ELKINGTON, J. St.C. (1952) *Proc. R. Soc. Med.*, **45,** 661.

GUILLAIN, G., and BARRÉ, J. A. (1936) *Rev. neurol.*, **65,** 573.

——, ——, and STROHL, A. (1916) *Bull. Soc. méd. Hôp. Paris.*, **40,** 1462.

HAYMAKER, W., and KERNOHAN, J. W. (1949) *Medicine, Baltimore*, **28,** 59.

LANDRY, O. (1859) *Gaz. hebd. Méd. Chir.*, **6,** 472.

LASSEN, H. C. A., IPSEN, J., and BANG, J. (1943) *Acta med. scand.*, **115,** 139.

LESCHKE, E. (1914) *Klin. Wschr.*, **51,** 783.

MILLER, H. (1956) *Proc. R. Soc. Med.*, **49,** 139.

PAPPENHEIMER, A. M., BAILEY, O. T., CHEEVER, F. S., and DANIELS, J. B. (1951) *J. Neuropath. clin. Neurol.*, **1,** 48.

SABIN, A. B., and ARING, C. D. (1941) *Amer. J. Path.*, **17,** 469.

SYMONDS, C. P. (1949) *Lancet*, ii, 677.

TYLER, H. R. (1957) *Medicine, Baltimore*, **36,** 147.


## Some Aspects of Referred Pain [*Abstract*]

By C. W. M. WHITTY, D.M., M.R.C.P.

*Oxford*

KELLGREN and Lewis in 1939 described referred pain of roughly segmental distribution from 6% saline injections into the interspinous ligaments. This work has been applied in the investigation and treatment of patients with persistent spontaneous pain and with known lesions of the pain pathways. The possibilities of referred segmental analgesia from similar injections of procaine have also been explored.

In the normal subject 6% saline will produce local stinging pain around the site of injection; it may also produce deep aching pain, skin hyperalgesia and palpable muscle spasm often bilateral and all within the same somatomeral segment as the injection. These effects can be rapidly reduced by the injection of 2% procaine into the site of saline injection.

In patients with spontaneous pain from post-herpetic neuralgia or painful scars, 6% saline in the appropriate interspinous ligament will aggravate the pain and hyperalgesia; 2% procaine if given two to five minutes later into the same site will abolish this aggravation and reduce the level of spontaneous pain, sometimes completely abolishing it. If procaine is given alone this also will reduce spontaneous pain but the effect is less marked

and less long-lasting than that of saline and procaine. When a series of such combin injections is given there may be permanent reduction and very occasionally permane abolition of spontaneous pain. In a patient with post-herpetic pain in the D3 and segments on the left, and angina of effort referred to the left arm, it was found that int costal nerve blocks of the herpetic area and procaine to the D3 and D4 interspinous lig ments each gave relief both of the herpetic pain and also of the angina of effort. Sali aggravated the post-herpetic pain but reduced the effort angina. Combined saline a procaine was more effective in relieving the herpetic pain and repeated injections ga permanent improvement.

In patients with spinothalamic tract lesions referred pain from mid-line saline injectio occurred only on the side with intact spinothalamic pathways. Referred sensation do occur to the other side, but it is a non-painful tingling. Bilateral unpleasant referre sensation, described subjectively as painful, was, however, noted in one such case: bu it was obtained only from the mid-dorsal segments and was unusually diffuse and referre deeply as "a feeling of being winded".

In one patient with a slight sensory level to both spinothalamic and posterior colum sense saline produced the expected segmental referred deep aching and muscle spasm, bu there was also a delayed severe skin hyperalgesia referred specifically to the upper limi of the clinical sensory level, seven or eight segments above the one injected.

It is emphasized that the referred effects of saline and procaine are inconstant. With apparently the same technique they may vary in the same patient on different occasions. In other patients they may not occur at all. Nevertheless they have potential therapeutic applications.

It is concluded that these observations lend support to the view of a sensory neurone pool in the spinal cord in which both summation and competition for a final common pathway may occur.

REFERENCES

KELLGREN, J. H. (1939) *Clin. Sci.*, **4**, 35.
LEWIS, T., and KELLGREN, J. H. (1939) *Clin. Sci.*, **4**, 47.

## Late Infantile Metachromatic Leucodystrophy

By MICHAEL JEFFERSON, D.M., M.R.C.P.
*Birmingham*

DIFFUSE cerebral sclerosis is a complex subject which has recently been well reviewed by Poser and van Bogaert (1956). It comprises a spectrum of diseases which have in common a general similarity of clinical and pathological outline, but they differ widely in detail, in their age of onset, time-span, inheritance or otherwise, and their microscopical anatomy, and they must differ too in their ætiology, though little enough is known at present of the cause of any of them. To some extent their classification is debatable, but broadly speaking they fall into three main categories. Firstly there is the group of conditions of which Schilder's disease is the prototype, secondly there is the class of subacute leuco-encephalitis and its analogues, and thirdly, there are the leucodystrophies, several types of which have been described whose affinities and distinctions are still not properly known.

### SYMPTOMATOLOGY

It is with the features of one form of the latter, namely late infantile metachromatic leucodystrophy that I want to deal. Examples of this malady have been described by several writers in the last twenty-five years, notably Greenfield (1933), Brandberg and Sjövall (1940), Brain and Greenfield (1950), Leslie (1952), Bertrand *et al.* (1954)[1] and Peiffer and von Hirsch (1955), and I have had recent personal experience of one case. In all of these, numbering 11 together, the correct diagnosis was only made after autopsy, but it ought not to be impossible to recognize (or at least suspect) the answer during life, if only the existence of the disease were more widely known, and the aim of this short paper is to draw attention to it as an entity.

Its semeiological pattern is a fairly constant one. The age of onset is commonly around 20 months, and the duration from first symptoms to death about 15 months. There is no evidence of sex predilection, nor much to suggest a familial tendency, but the data on the latter point are not fully satisfactory, since a majority of case reports have related to children without sibs. From the symptomatic point of view, the onset is most often with vague

[1]The case described by these writers was originally stated to be non-metachromatic, but metachromasia was found on re-examination by Diezel (1957).

fretfulness and slight disorder of gait, so that the child is no longer so confident on its feet as before. Insidiously over the course of a few months, the power to walk, or even to stand, is completely lost, and the upper limbs, neck and trunk muscles become considerably weakened as well, so that use of the arms, sitting without support, or even holding the head up, is difficult or impossible. At about this stage, as in one of Brain and Greenfield's cases, in my own, and perhaps in Leslie's case too, there may be general hypotonicity along with the loss of muscular strength, so that the child's appearance may call to mind some form of myopathy. This phase, however, may not be present, and in any event is transitory, soon passing into stiffness of the limbs, with extended legs and feet in equinovarus and the arms flexed. The tendon reflexes as a rule are by now unobtainable and the plantar reflexes upgoing. Sudden and frequent accessions of muscle spasm become noticeable, which exaggerate pre-existing hypertonus of the limbs, and produce bodily attitudes resembling experimental decerebrate rigidity. They are apt to be induced by any external stimulus or occur spontaneously, are usually accompanied by crying, and may last many minutes at a time. Meanwhile cranial nerve signs have also developed, in the form of ptosis or nystagmus or both. The appearance of the latter can vary from fine rapid shimmering to slow rhythmic to-and-fro jerking, and it may be paroxysmal or continuous. All this time, too, the child's mental state has been gradually dilapidating. Initial seeming disinclination to speak has, by stages, become a definite poverty of words, and ultimately a global aphasia, and what was at first a mild lack of interest in surroundings has turned into profound apathy towards people and objects. Signs to suggest blindness and deafness of cortical origin declare themselves, and feeding becomes increasingly difficult. The child has now arrived at a state of frank decerebration in which it may remain for a number of weeks before death comes finally from failure of the medullary centres, perhaps with terminal bronchopneumonia.

## Differential Diagnosis

As to differential diagnosis during life, there are not many possibilities which have to be considered. The relatively slow march of the disease, and its ingravescent onset, rule out any of the ordinary forms of virus encephalitis or allergic encephalomyelitis. It is less easy to exclude subacute sclerosing or inclusion body encephalitis, but the recorded cases of these conditions have been in older age groups, and furthermore, more or less rhythmically recurrent and symmetrical myoclonic jerkings of the limbs, trunk and head are found in them which are not a feature here. Both also show rather characteristic EEG phenomena in the shape of repeating high amplitude complexes, appearing every few seconds against a relatively flat potential background. The only available EEG data in metachromatic leucodystrophy seem to be in my own case, where serial traces showed not this pattern, but a general dysrhythmia which came to be increasingly dominated by delta activity, with some scattered sharp waves at a late stage. If this can be taken as a paradigm, then it suggests that the electrographic signs can be useful in differentiation. Another small point of distinction is the C.S.F., for in leucodystrophy the protein is raised, usually with increased globulin, and without cellular increase, but the Lange curve does not show the first zone precipitation met in inclusion and sclerosing leuco-encephalitis.

That leaves over Schilder's disease which can only be distinguished at autopsy or perhaps by cerebral biopsy, and cerebral lipidosis such as amaurotic familial idiocy, but there the early presence of retinal pigmentary change or macular spot should usually allow recognition.

## Pathology

Pathologically the gross appearance of the brain is normal, though in handling it feels unduly resilient. Microscopic sections show that there is massive demyelination in the cerebral hemispheres, which includes the internal capsule and corpus callosum but tends to spare the juxta-cortical arcuate fibres, and the fibres of the optic radiation; there is also fall-out of intracortical radial fibres. The white matter of the cerebellum suffers heavily, too, and so do the descending fibre systems of the brain-stem and spinal cord. The destructive process is one which affects axones as well as their myelin sheaths, and there is pronounced overgrowth of fibrillary astrocytes. There is relative absence of sudanophil products of myelin breakdown, and a striking feature is the scattering of unusual granular material throughout the zones of white matter damage. It is mostly visible in rounded clumps, the so-called granular bodies, in some of which a nucleus can be made out, and it is evident that they represent degenerate microglial phagocytes. It is also seen discretely as a finer dusting, and may be found occasionally in the cytoplasm of swollen astrocytes and within the bodies of some nerve cells. It exhibits the property of staining metachromatically, in various shades of pink or dull red with toluidine blue, instead of giving the normally expected (orthochromatic) blue coloration. Histochemically it is a lipid substance, probably not a single one but of two or three different kinds, one at least being a glycolipid.

### Pathogenesis

There is uncertainty about the origin of this material. There is a metachromatic phase in the breakdown of myelin in normal (Wallerian) degeneration of nerve fibres, although it is only transitory (Einarson and Neel, 1942), and it might therefore arise from arrest of myelin catabolism short of its ordinary end-point because of an enzyme defect. This notion was favourably considered by Kaltenbach (1922), though he also put forward as an alternative the possibility of a fault in myelin anabolism, leading to accretion of a substance impossible to be dealt with further by normal metabolic routes. The trend of current opinion, however, is to interpret it as deriving from an inborn error of lipid manufacture in the nervous system, affecting myelin synthesis tangentially instead of in the direct line (Diezel, 1957).

This thesis naturally suggests that late infantile metachromatic leucodystrophy may have nosological alignment with the cerebral lipidoses as a general class, a notion that was originally discussed in a different context by Witte (1921) and more recently by Norman (1947), and it has received some biochemical support from the studies of Edgar (1957). Whether the presence of metachromatic material in the viscera, which has been noted in several cases (Brain and Greenfield, 1950; Leslie, 1952; Bertrand *et al.*, 1954), can be taken as an index of widespread lipid mishandling is not yet clear, and it may only represent an overflow phenomenon. Nevertheless the relatively frequent existence of renal deposits is of practical importance, as it provides a possible method for diagnosis of the disease during life by examination of the urine, and Austin (1957) has just reported a technique which he has developed and used successfully.

The recently published report of the Antwerp colloquium (van Bogaert *et al.*, 1957) gives promise that we are now on the edge of clearer understanding of the leucodystrophies, from information obtained by the use of new histochemical and biochemical techniques to eke out the findings of classical morbid anatomy. It now seems certain that the late infantile type of metachromatic leucodystrophy is distinct both in microanatomy and histochemistry (Diezel, 1957) from the acute infantile globoid cell leucodystrophy of Krabbe type, though it may not be so sharply divided from the juvenile forms described by Scholz (1925) and others, or the chronic cases recorded by Witte (1921), Carrillo (1934), van Bogaert and Dewulf (1939) and Norman (1947), in spite of their pronounced clinical differences. Further, the work of von Hirsch and Peiffer (1957) indicates that the histological division of metachromatic from non-metachromatic leucodystrophies, having the same morphological characteristics otherwise, is invalid. Lastly, with reference to the absence of the oligodendroglia in late infantile metachromatic leucodystrophy, which has been suspected as a possible prime factor in its causation, no definite answer is yet possible, but recent evidence diminishes the likelihood of their being directly concerned.

### References


Austin, J. H. (1957) *Neurology*, **7**, 415, 716.

Bertrand, I., Thieffry, S., and Bargeton, E. (1954) *Rev. neurol.*, **91**, 161.

Brain, W. R., and Greenfield, J. G. (1950) *Brain*, **73**, 291.

Brandberg, O., and Sjövall, E. (1940) *Z. ges. Neurol. Psychiat.*, (Orig.), **170**, 131.

Carrillo, R. (1934) *Sem. méd., B. Aires*, **41**, ii, 938.

Diezel, P. B. (1957) *In:* van Bogaert *et al.* (1957), p. 52.

Edgar, G. W. F. (1957) *In:* van Bogaert *et al.* (1957), p. 186.

Einarson, L., and Neel, A. V. (1942) *Acta jutlandica*, **14**, 2.

Greenfield, J. G. (1933) *J. Neurol. Psychopath.*, **13**, 289.

Hirsch, T. von, and Peiffer, J. (1957) *In:* van Bogaert *et al.* (1957), p. 68.

Kaltenbach, H. (1922) *Z. ges. Neurol. Psychiat.* (Orig.), **75**, 138.

Leslie, D. A. (1952) *J. Path. Bact.*, **64**, 841.

Norman, R. M. (1947) *Brain*, **70**, 234.

Peiffer, J., and Hirsch, T. von (1955) *Excerpta med., Amst.*, Sect. VIII, **8**, 802.

Poser, C. M., and Van Bogaert, L. (1956) *Acta psychiat., Kbh.*, **31**, 285.

Scholz, W. (1925) *Z. ges. Neurol. Psychiat.* (Orig.), **99**, 651.

van Bogaert, L., Cumings, J. N., and Lowenthal, A., eds. (1957) Cerebral Lipidoses, a Symposium. Oxford.

——, and Dewulf, A. (1939) *Arch. Neurol. Psychiat., Chicago*, **42**, 1083.

Witte, F. (1921) *Münch. med. Wschr.*, **68**, 69.

*Proceedings of the Royal Society of Medicine*

Vol. 51
163

# Section of Obstetrics and Gynæcology

President—Sir ARTHUR GEMMELL, M.C., T.D., M.A., M.D., Hon. M.M.S.A., F.R.C.S.Ed., F.R.C.O.G.

[*November* 22, 1957]

## DISCUSSION: THE BREECH

**Dr. G. F. Abercrombie** (London):

*The Timing of External Version*

Everyone would agree that a normal vertex presentation in the care of an unaided midwife is a very much safer proposition that a breech delivery in a specialist hospital [1], but we all know that some breech presentations, if allowed to persist too long, cannot be converted to vertices, even with the help of anæsthesia. The question is whether, by care and thought, a breech presentation, if it be the only complication, can invariably be avoided. In 1939, I advocated early external version [2], i.e. about the 30th to 32nd week, and up to that time all my private patients, 180 in number, had presented a vertex at confinement, although a breech presentation had been observed during pregnancy in 36, and external version had seemed to be necessary in 16.

In the 100 confinements which I have since attended, there were two breech deliveries, one in a primigravida who was overdue and the other in a multipara already in labour when first seen. There were 32 other breech presentations. Of these, 16, including one twin, assumed, unaided, a final vertex position by or shortly after the 32nd week; in 10 others, one of which required an anæsthetic, a single external version was done, and the resulting vertex presentation persisted, as far as I know without relapse, until delivery. My present policy is to watch these patients very carefully from the 30th week onwards. If, on any given occasion, I think I could turn easily, I wait another week, but as soon as I feel that, if left any longer, I might fail without anæsthesia, I turn at once. Before resorting to anæsthesia, I try to turn on two or three occasions at intervals of two or three days. Quite often, if I fail at a first attempt, I may succeed a little later.

There remain 6 pregnancies in which spontaneous version from breech to vertex had already taken place, but in which the breech presentation reappeared. In 3 of these a single external version was enough. The next, a 4-para, showed a very unstable presentation.

In her third pregnancy spontaneous version to vertex was noted at the usual time, normal labour occurred two days early, the baby weighed 5 lb. 15 oz., and the cord was tightly round the neck two and a half times. In the next pregnancy, a breech presentation recurred and persisted into the 36th week, when it was corrected. Two more spontaneous versions and two more external versions brought us to the 41st week, when I invited a consultant to see her. He queried her dates, but consented to a final external version followed immediately by induction with a Drew Smythe catheter. Three days later she delivered herself and the baby weighed 5 lb. 12 oz.

I never discovered why this presentation was so unstable, but I do not believe it was because the cord was round the neck once. The last patient set me a series of problems.

In her first pregnancy, she took me completely by surprise, for a breech was found in the 39th week long after spontaneous version from breech to vertex had taken place; in her second, similarly, external version corrected a relapsed spontaneous version. I know nothing of her third pregnancy, after which, on account of backache, repeated miscarriages and a retroverted uterus, a Gilliam's operation was done. She soon became pregnant again. The fœtus was uncommonly mobile and the cervix, naturally, very high in the pelvis. After three versions between the 32nd and 36th weeks, a vertex was found consistently until she was a week overdue, when the breech presentation

unexpectedly recurred and was corrected. Fortunately she went into labour a few days later and the baby weighed 9 lb. 4 oz. The same sort of thing occurred in her final pregnancy for the breech presentation recurred in the last week before term, but could not be turned without anæsthetic. Accordingly, after consultation, external version was done under an anæsthetic, and a pint and a half of liquor amnii was drawn off with a Drew Smythe catheter. Even then, and in spite of a firm binder, the head, still very high, tended to float away into an iliac fossa. Delivery was easy and the baby weighed 8½ lb., but the cervix was torn on both sides and a very severe post-partum hæmorrhage followed, which required another anæsthetic and a blood transfusion. Perhaps we tried to be too clever.

My conclusion is that, if one has the opportunity to observe a single fœtus in a normal uterus from the 30th week onwards, breech presentation can, when necessary, be eliminated, usually by a single well-timed external version. On rare occasions only the manœuvre must be repeated, the possibility of the cord being tightly round the neck being borne in mind [3]. I admit that, in order to be sure of eliminating the 3% or 4% which would otherwise persist, I find myself constrained to perform version in a high proportion, but as anæsthesia is so seldom required, the obstetric gain is very great. Even when the obstetric factors are thoroughly unfavourable, a vertex presentation can always be obtained, but whether, when confronted with an unusually unstable presentation, it is wise to induce labour, simply in order to expedite delivery, is a much more doubtful proposition.

*The figures for the two series together are as follows:*

| | | | | |
|---|---|---|---|---|
| Pregnancies | | | | 280 |
| Breech presentation | | | 70 | |
| Corrected by spontaneous version | | 37 | | |
| Corrected by external version | | 31 | | |
| Without anæsthetic | 27 | | | |
| With anæsthetic | 4 | | | |
| Too Late! Therefore breech delivery | | 2 | | |

REFERENCES

1 An Obstetric Survey by Members and Associates of the South-West of England Faculty of the College of General Practitioners, Supplement to the Research Newsletter, May 1957. The Devonshire Press, Torquay.

2 ABERCROMBIE, G. F. (1939) *Proc. R. Soc. Med.*, **32**, 911.

3 WALKER, C. W. (1956) *Proc. R. Soc. Med.*, **49**, 915.

**Mr. John Hamilton** (Liverpool):

In 1933 the late Dr. J. W. Burns and Dr. Charles McIntosh Marshall evolved a technique of breech delivery which, with slight modifications, has been the method used in the Liverpool Maternity Hospital from that time. The background of the method of delivering the aftercoming head has an interesting story attached to it. The late Dr. Burns was endeavouring to deliver an aftercoming head through the brim and eventually gave it up as hopeless. He had watched the infant hanging down for some time when suddenly the infant appeared to drop. Seizing it by the legs he swung it up and over the mother's abdomen and to his surprise delivered it with great ease.

In the first twenty-four years of this method of delivery there have been 1,306 infants weighing over 4·9 lb. delivered by the vaginal route as a breech. The fœtal mortality during that period has been 4·2% but there has been a steady improvement throughout the period and the fœtal mortality for the past five years has been 2%. As, during these twenty-four years, there have been some 30+ registrars who are mainly responsible for the deliveries and some of whom have not had any great experience of breech delivery I feel that it speaks well for a routine that has been evolved over the past twenty-four years.

I feel that it should be accepted that elderly primigravida and any long-standing case of infertility should not be allowed to have a vaginal delivery.

A careful assessment of the pelvis clinically and, if necessary, radiologically is essential, In addition, an estimation of the size of the infant is desirable. An obviously small pelvis with a large infant may well contra-indicate vaginal delivery. I do not believe that a large infant *per se* is a cause for alarm—it is the relative size of the infant and pelvis that matters.

There is a widespread belief that there is more difficulty in the delivery of a breech with extended than with flexed legs. Given a reasonable size of infant and pelvis, labour, in the case of the extended legs, is slightly more rapid. This is explained by the fact that the breech with extended legs fits well into the lower segment and acts as a perfect dilator of the cervix.

The average length of labour where the legs are extended is one hour less than when they are flexed. This is important in the conduct of the modified trial of labour in a breech since the trouble met with in breech with extended legs increases in direct ratio with the length of labour. If the length of the first stage of labour in a breech with extended legs is unduly prolonged it means that one is either faced with an inco-ordinate uterine action, or there is uterine inertia usually due to an excessive size of the infant. I have always been impressed with the comparatively infrequent uterine inertia in breech presentations unless the breech is of a large size, which has convinced me that most of the so-called inco-ordinate uteri have some underlying factor present.

Prolonged labour, whether the breech or the vertex is presenting, will give a high risk to the fœtus and may require a decision to change the mode of delivery from vaginal to abdominal. As I have mentioned earlier the size of the infant should be assessed clinically and radiologically. If the impression is one of great size, a trial labour of the modified form is started but at any time preparations are made for Cæsarean section. During the past twenty-four years, 214 Cæsarean sections have been done in the Liverpool Maternity Hospital for breech presentation. Of these there were 66 done on account of age, 61 because of contracted pelvis and 49 because of large infant and inertia.

The large infant that is going to give rise to trouble, fortunately in nearly every instance, shows its size by producing a uterine inertia. If the infant is evidently large, the cervix ripe and the breech fitting the cervix well, there is a place for induction of labour before term. This is, I feel, a safe procedure in case of breech with extended legs and if the conditions for induction are satisfied at the 38th week, there is I feel no contra-indication and, in fact, many advantages where an obviously large infant is present.

I will say at the outset that there is only one place for breech delivery, whether multigravida or primigravida, and that is in hospital.

The conduct of the 1st stage of labour is largely that of the conduct of a normal vertex, bearing in mind the fact that uterine inertia is an unfavourable sign and may lead one to consider whether a vaginal delivery is really the correct method to be employed.

The conduct of the 2nd stage can be divided into the expulsive part and the actual delivery. It is, I believe, important not to encourage a patient to bear down until it is certain that the cervix is fully dilated. This is especially important in cases of breech with flexed legs as, with prolapse of the foot through the cervix into the vagina, the patient may feel a desire to push although the cervix is not fully dilated. There is undoubtedly no more important cause of trouble, especially with the arms, than an incompletely dilated cervix.

At the Liverpool Maternity Hospital I found that the average length of the second stage was one hour. Where the second stage was unduly prolonged there was an increase in the number of stillbirths; some of these were due to faulty selection of cases for vaginal delivery but some were due to fœtal anoxia during prolonged labour. Therefore, an unduly prolonged second stage should be a warning. Delay in the second stage is due to a faulty selection of case, namely, too large a baby for too small a pelvis, or to the splinting action of the extended legs not allowing the lateral flexion of the trunk. If there is delay in the second stage a decision must be made between breech extraction and Cæsarean section.

We must now turn to the actual delivery of a breech and the method I propose to describe is, in the main, the Burns-Marshall technique. We find that very soon after full dilatation, the anterior buttock will be visible at the vulva and then the patient is encouraged to bear down. She is thus encouraged until the anus is visible. At this stage the time for delivery is at hand and the patient is placed in the lithotomy position. I would like to stress again that a breech delivery should be a set operation and, in my opinion, partly conducted under anæsthesia which should be complete by the time the shoulders are born.

When the buttocks are distending the perineum and the anus is visible is the time for the performance of an episiotomy. This is done after infiltration along the line of incision with 1% procaine. The actual incision of the episiotomy is timed to coincide with an expulsive effort on the part of the mother. Further expulsive efforts on the part of the mother will push both buttocks past the vulva but it may be necessary at this stage to assist slightly by gentle groin traction. After the buttocks are born the thighs can then be abducted and the knees flexed thus delivering the body to the umbilicus. At this stage a loop of cord is pulled down, largely to make certain that there is sufficient free cord to make delivery uncomplicated by cord entanglement. At this stage, also, anæsthesia is induced with intravenous Pentothal.

From this stage we have to complete the delivery, avoiding extended arms and an extended head. It is extremely rare to see extended arms in a radiograph of a breech and it is my belief that they are more often produced by faulty technique. The commonest cause of producing extended arms is bringing the shoulders through the brim in the transverse diameter.

After anæsthesia has been induced, the child is grasped either by the feet or by a grip of the thighs using a sterile towel to avoid the slippery surface which is produced by meconium, and not to prevent premature inspiration. Steady—and I emphasize steady—traction is now exerted towards the floor. This traction is continued until the anterior scapula appears. Considerable force is used during this traction. Once the scapula appears, the anterior arm can be released by hooking it out with the fingers. As soon as the anterior arm is released the child is lifted upwards by the legs away from the side on which the back is situated and the posterior arm is gently extracted.

The child is then allowed to hang down in order that its body weight may aid flexion. This will aid in the engagement of the aftercoming head. There seems to be some doubt about how long the body is allowed to hang. I think I can safely say that we allow it to hang while we wash the meconium off our gloves. If the head is not descending it may be necessary to apply suprapubic pressure. This should be done with care and the knowledge that the flexion is required for the head to pass through the pelvis satisfactorily. There should, therefore, be more pressure on the sincipital than the occipital side in order to favour this flexion. When it is clear that the head has entered the cavity of the pelvis the infant is grasped by the feet and, maintaining traction, the feet are brought up in a wide arc through 180 degrees. Traction at this stage is essential in order that the head can pass through the pelvis in flexion. If no traction is applied and the feet merely lifted up over the mother's abdomen, the neck of the fœtus will be broken. At the same time that traction is applied I usually keep up suprapubic pressure as I believe that flexion can be maintained more easily that way. When this traction through 180 degrees is complete the mouth will be appearing at the vulva and either by pulling back the perineum or putting in a Sim's speculum, an airway can be provided. I, personally, at this stage always apply Simpson's forceps as a routine. The main advantage to the aftercoming head of forceps is the absolute control one can obtain over the rate of exit.

Some of the damage to the fœtal skull can be caused by a sudden rebound of the skull from a very rapid exit and as once the mouth is at the vulva there is ample time for delivery, advantage should be taken of this available time.

In summary, I would like to emphasize one or two points which I think are essential in breech management:

(1) Careful selection of cases for vaginal delivery.
(2) Regard breech delivery as a set operation requiring a team of obstetrician, assistant and anæsthetist.
(3) Rapid induction of anæsthesia as a routine in all breech delivery—it is often too late, if trouble is encountered, to start induction.
(4) Careful guidance of the shoulders through the brim.
(5) Allowing the body weight to bring the head through the brim.
(6) Firm traction on legs bringing head to the outlet.
(7) Forceps to the aftercoming head more to control rate of exit than to speed rate of exit.
(8) And finally, and most important of all, traction, when applied, should be even and not jerky.

REFERENCES

BURNS, J. W. (1934) *J. Obstet. Gynæc., Brit. Emp.*, **41**, 923.
MARSHALL, C. M. (1934) *J. Obstet. Gynæc., Brit. Emp.*, **41**, 930.

**Mr. J. H. Peel** (London):

I wish to discuss the part played by external cephalic version as a means of lowering firstly, the incidence of, and secondly the overall fœtal loss due, to breech delivery.

*The Justification for External Cephalic Version*

The paper published by Vartan (1945) established external cephalic version as a sound physiological procedure. He emphasized that up to the 32nd/33rd weeks of pregnancy, it was normal for the baby to lie as a breech, but that by that date the majority of these had undergone spontaneous cephalic version. A small percentage, unable to turn spontaneously, remain, either because there is very little liquor, or as the result of the legs being extended so that the breech engages in the pelvis by the 32nd week. In performing external cephalic version, one is simply aiming to mimic the natural process of spontaneous version, and the timing of this procedure may have to be varied, depending on the amount of liquor, size of baby and the tone of the uterine muscle. It is seldom advisable before 33 weeks, but in the primigravida it should not be left after the end of the 35th week. White (1956) showed that spontaneous version does occur in some 30% of primigravidæ after the 34th week, but hardly ever after the 36th week.

The dangers of external cephalic version to the fœtus have been emphasized by several writers, particularly if anæsthesia is used. Nevertheless there are several series of cases

published which show that these dangers can be reduced. Clayton and Peel (1948) 1·7% fœtal loss. Freeth and MacVine (1951) 1·4%. Dalley (1952) no fœtal loss in 330 cases of external version without anæsthesia.

Table I shows my personal series of 1,089 cases over a ten-year period 1947/57, and the

TABLE I.—MATERIAL ANALYSED. ALL BOOKED CASES

| | Total deliveries | Version attempted | Anæsthesia used | Successful version | Fœtal loss due to version |
|---|---|---|---|---|---|
| (1) Personal Series 1947/1957 | 1,089 | 52=4·8% | 6=11·5% | 49=94·2% | 0 |
| (2) K.C.H. Series 1949/1957 | 7,816 | 411=5·2% | 147=35·7% | 375=91·2% | 6=1·4% |

second series of 7,816 booked cases at King's College Hospital between 1949 and 1957. In my own series version failed in 3 cases, 2 of which were subsequently delivered by Cæsarean section for placenta prævia and age, and in only one was vaginal breech delivery necessary. In my own series there was no fœtal loss due to version, but in the K.C.H. series there were 6 babies lost, giving a total of 1·4% (Table II). Two of these can, however, be excluded as version did not cause fœtal death, which reduces the mortality to 0·9%.

TABLE II.—K.C.H. SERIES. STILLBIRTHS PRESUMED DUE TO EXTERNAL CEPHALIC VERSION

(6=1·4%)

3 No Anæsthetic 1·1%

3 With Anæsthetic 2·0%

| | | | | |
|---|---|---|---|---|
| 1 | Intra-uterine death | 32 weeks | No anæsthetic | |
| 2 | Intra-uterine death | Version 32 weeks | No anæsthetic. | I.U.D. at 34 weeks |
| 3 | Intra-uterine death | 32 weeks | With anæsthetic | |
| 4 | Intra-uterine death | Version 36 weeks | No anæsthetic. | I.U.D. at term |
| 5 | Intra-uterine death | Version 36 weeks (twice) | With anæsthetic | |
| 6 | Intra-uterine death | Version 38 weeks | With anæsthetic | |

The second argument which is used against external cephalic version is that it fails to lower the incidence of breech delivery at term because of the high incidence of spontaneous version. The incidence of breech delivery at term is between 3% and 4% in institutions not practising external cephalic version. Table III shows that in 7,816 total deliveries

TABLE III.—K.C.H. SERIES. SINGLE BREECH DELIVERIES (AFTER 34 WEEKS' GESTATION)

| Total deliveries | Breech deliveries | Failed E.C.V. | E.C.V. not used | Undiagnosed before labour |
|---|---|---|---|---|
| 7,816 | 77=0·98% | 36 | 29 | 12 |

there were 77 single breech deliveries after 34 weeks, i.e. below 1%. External cephalic version failed in 36 cases, in 29 it was not attempted, and in 12 the diagnosis was missed before the onset of labour. In my own series there were only 5 breech cases, an incidence of 0·5% (in addition to the 3 cases mentioned above, there were 2 delivered by Cæsarean section in which external cephalic version was not used). Fell (1953) showed an incidence of breech delivery of 1·35% in an institution performing routine external cephalic version. White (1956) attempted to prove that even after 34 weeks spontaneous cephalic version occurs so frequently (50% approx.) as to make external cephalic version by the obstetrician unnecessary. The figures that he quotes, an incidence of breech delivery of 3·2% after the 34th week, completely disprove the very point which he set out to make.

Another argument that is used against external cephalic version is that the results of vaginal breech delivery are now so good that it is not necessary to do it. However, the low fœtal mortalities quoted (between 1% and 3%) have been achieved in two ways:

(1) By emphasizing the abnormality of breech presentation, to the extent that senior and experienced obstetricians are always present at the delivery.

(2) By such careful selection of cases for vaginal delivery that the Cæsarean section rate is very high. Table IV shows that in one series it is 12·4%, and in the series of Law

TABLE IV.—CÆSAREAN SECTION RATE (BREECH PRESENTATION)

| Authority | Total cases | Cæsarean section % |
|---|---|---|
| Cox (1950) | 1,004 | 12·4 |
| Law (1955) | 136 | 13·3 |
| White (1956) | 277 | 9·0 |
| Peel (1957) | 411 Attempted E.C.V. | |
| | 29 No E.C.V. | |
| | 12 Not diagnosed antenatally | |
| | 452 | 5·7 |

TABLE V.—STILLBIRTHS SUBSEQUENT TO EXTERNAL CEPHALIC VERSION

| | |
|---|---|
| 3 | Breech deliveries at term. |
| 2 | Abnormal fœtuses. |
| 3 | Severe pre-eclamptic toxæmia developing later. |
| 3 | Prolonged labour as vertices at term. |
| 2 | Late neonatal deaths unrelated to version or delivery. |
| 6 | Presumed due to external cephalic version. |
| Total 19 | |

TABLE VI.—K.C.H. SERIES. EXTERNAL CEPHALIC VERSION UNDER ANÆSTHESIA. 147 CASES

| Weeks gestation | Total cases | Successful | |
|---|---|---|---|
| 32–33 | 7 | 5=71·4% | 50=86·2% |
| 34–35 | 51 | 45=88·2% | |
| 36–37 | 55 | 34=61·8% | 61=68·5% |
| 38–T | 34 | 27=79·4% | |

(1955) it is 13·3%. It is usually stated that the indication for Cæsarean section is not the breech presentation but an associated condition such as contracted pelvis. However, had the baby been presenting as a vertex, vaginal delivery would often have been possible. The weakest link in the argument that a breech is as safe as a vertex delivery is the readiness with which Cæsarean section is undertaken. By way of contrast I have worked out the incidence of Cæsarean section in our own group of cases, which would have reached term as breeches had external cephalic version not been carried out. There is an incidence of Cæsarean section of 5·7%, which includes 9 after successful version, which is about half the usually quoted figures in institutions not practising external cephalic version.

It is argued that if external cephalic version is used routinely, the number of breech deliveries that become available for teaching students, residents and registrars will be very limited. This is not a justifiable argument, and negatives the whole purpose of antenatal care.

By way of conclusion I would like to stress a few of the important points relative to external cephalic version:

(1) Early diagnosis of the breech presentation is essential (32 weeks in the primigravida). When there is relatively little liquor, a deeply engaged breech with extended legs at 32 weeks is easily missed, and that is just the case in which early version is essential if it is to succeed. It should be attempted in the first instance without anæsthesia, but with anæsthesia at or very soon after the 34th week.

(2) In performing external version, work mostly on the breech rather than on the head. The direction for version is the one in which the baby will most easily turn, and frequently when the legs are extended in a primipara, the baby turns more easily if it is moved, not in the direction in which it is looking, but in the opposite one.

(3) Anæsthesia. We have employed succinyl choline hydrochloride (Scoline) 50 mg., after the patient has received premedication with Omnopon or pethidine, and been put to sleep with a small dose of Pentothal. Ether anæsthesia is rarely necessary.

(4) It requires just as much skill and experience to know when to desist from attempts at external version as it does to know when to undertake vaginal breech delivery. Too much force is unnecessary.

(3) There are certain definite contra-indications to external cephalic version:
(i) Pre-eclamptic toxæmia because of the danger of placental separation.
(ii) Suspected cases of placenta prævia.
(iii) A scar in the uterus from previous classical Cæsarean section or myomectomy.
(iv) A congenitally abnormal fœtus.
(v) Any associated condition which necessitates Cæsarean section in any case.
(vi) Multiple pregnancy.
(vii) Unicornuate uterus.

Inevitably there must remain a hard core of breech cases where version is either contra-indicated or fails. It is important to assess all cases with special reference to contraction of the pelvis. A breech delivery is relatively safe if there is a roomy pelvis, but it is a highly dangerous procedure if the pelvis is contracted. In cases of minor degrees of contraction of the pelvis or an abnormally large baby, it is wiser to err on the side of doing a Cæsarean section rather than risk vaginal delivery, but it is particularly in this last group of cases that external cephalic version really does justify itself. Minor degrees of contracted pelvis which are suitable for a trial of labour if the presentation is a vertex, and which so often end in successful vaginal delivery, are the most frequent cause of fœtal death in this type of breech delivery. If the incidence of Cæsarean section is to be kept within reasonable limits, external cephalic version should certainly be attempted in this group of cases.

## REFERENCES


Cox, L. W. (1950) *J. Obstet. Gynæc. Brit. Emp.*, **57**, 197.
—— (1955) *J. Obstet. Gynæc. Brit. Emp.*, **62**, 395.
Clayton, S. G., and Peel, J. H. (1948) *J. Obstet. Gynæc. Brit. Emp.*, **55**, 613.
Dalley, O. (1952) *J. Obstet. Gynæc. Brit. Emp.*, **56**, 841.
Fell, M. R. (1953) *Lancet*, ii, 364.
Freeth, D., and MacVine, J. S. (1951) *Brit. med. J.*, ii, 881.
Law, R. G. (1955) *J. Obstet. Gynæc., Brit. Emp.*, **62**, 614.
Vartan, C. K. (1945) *J. Obstet. Gynæc. Brit. Emp.*, **52**, 417.
White, A. J. (1956) *J. Obstet. Gynæc. Brit. Emp.*, **63**, 706.


**Mr. David Methuen** (Oxford):

I should like to present a series of cases of breech deliveries conducted in the Area Department at Oxford and to discuss the problem of anæsthesia for this type of delivery.

During the five years from the beginning of 1952 to the end of 1956 there were 448 breech deliveries out of a total of 15,500: an incidence of 2·9%.

There were 48 stillbirths and 25 neonatal deaths giving an uncorrected perinatal mortality of 16·3% compared to an overall fœtal loss of 3·5%. The Cæsarean section rate was 8% and there was no maternal death.

Table I shows the fœtal loss for mature and premature babes of primiparous and multiparous patients:

TABLE I

| PRIMIPARÆ | | MULTIPARÆ | |
|---|---|---|---|
| | >5 lb. 8 oz. | | >5 lb. 8 oz. |
| 139 | 4 Stillbirths | 156 | 8 Stillbirths |
| | 0 Neonatal deaths | | 2 Neonatal deaths |
| PERINATAL MORTALITY .. | 2·8% | PERINATAL MORTALITY .. | 6·4% |
| | <5 lb. 8 oz. | | <5 lb. 8 oz. |
| 50 | 9 Stillbirths | 103 | 27 Stillbirths |
| | 8 Neonatal deaths | | 15 Neonatal deaths |
| PERINATAL MORTALITY .. | 34% | PERINATAL MORTALITY .. | 40·7% |

In these 448 deliveries general anæsthesia, local analgesia, or a combination of the two was used 208 times. More than half the cases required only general analgesia.

Pudendal block was used for 37·5% of the deliveries and I would suggest that, in the interests of the mother and baby, this method of analgesia or epidural analgesia should be used more frequently for the following reasons, which should be emphasized and re-emphasized.

Firstly the risk of inhaling regurgitated stomach contents is eliminated and secondly transplacental narcosis is diminished. This is particularly important for the premature baby and Hingson (1947) has shown how the premature neonatal death-rate can be reduced by using caudal analgesia. Prematurity is a common complication of breech delivery and it occurred in 34% of the cases in this series.

During the last twelve months in our unit at the Radcliffe Infirmary 90% of all operative vaginal deliveries and 93% of breech deliveries have been performed either under pudendal block or epidural analgesia.

For an assisted breech delivery local infiltrative analgesia is the safest method to use and in my opinion is the anæsthetic of choice for such deliveries. The method used is to combine blocking the pudendal nerve with paravaginal and perineal infiltration. Under it forceps may be used to deliver the after-coming head and an episiotomy can be made and repaired painlessly. We have now used epidural analgesia 339 times in all and our experience with it for 24 breech extractions without fœtal loss has been very satisfactory. The technique employed is to insert a number 15 Lauer caudal needle through the sacro-coccygeal membrane. A fine nylon tube is passed through the needle which is then withdrawn. For effective analgesia to be obtained the tube must be passed for a distance of 5 to 6 in. so that the injection will be made above the lumbo-sacral junction. Below this the level of analgesia may be inadequate. A test dose of 2 c.c. of anæsthetic solution is injected. If the theca has been inadvertently punctured spinal anæsthesia will result. That this has not happened is checked after three minutes by demonstrating movements of the legs and feet.

The full anæsthetic dose of 20–25 ml. of 1% Xylocaine and adrenaline 1 : 100,000 is injected. Within minutes, using this preparation, analgesia is induced adequate for dealing with any difficulty associated with extended legs, the arms, or the after-coming head, and the operating conditions are ideal.

May I now stress the dangers and difficulties of this method?

Firstly the technique of correctly inserting the needle must be learned. Once the "feel" of this has been acquired the number of humiliating failures will be small.

Inserting needles and tubes carries the risk of these breaking. The nylon tubing can be autoclaved and is very tough. A tube of inferior plastic material was broken once in our series, but this has not occurred since we used nylon.

Total spinal anæsthesia is a potential risk, but should not happen if the initial test dose is carefully made.

Sepsis has not been encountered and hypotension has given rise to no concern since the dose was reduced to 20–25 ml. of anæsthetic solution.

These complications emphasize that this method of analgesia should only be used where the necessary equipment and assistance are available to deal with them.

The only alternative for breech extraction is to use either spinal or general anæsthesia; both are best avoided.

Particularly to be condemned is to allow partial delivery to occur under local anæsthesia and then, with the patient in discomfort, distress and the lithotomy position, to induce general anæsthesia. At the end of labour, possibly with the gut dilated, the stage is set for an anæsthetic tragedy.

The recent report on maternal mortality has emphasized the dangers of anæsthesia in obstetrics and I feel sure that the avoidance of general anæsthesia and the more extensive use of local analgesia will minimize this risk in breech delivery.

I should like to thank Dr. R. Bryce Smith and Dr. J. V. Mitchell for their help and I am deeply indebted to Mr. J. Stallworthy and Mr. W. Hawksworth.

REFERENCE

HINGSON, R. A. (1947) *Curr. Res. Anesth.*, **26**, 177.

**Mr. C. K. Vartan:**

From an examination of the earlier figures at the British Hospital for Mothers and Babies it was clear that the bulk of the babies lost were in assisted deliveries. I therefore planned to induce labour in all failed version cases at the 38th week, with the object of producing smaller babies which would not need to be extracted. I have a twenty-years' experience of this practice.

A recent analysis covering ten years shows that 85 or 37·6% of the whole were induced; 62·4% were not. One fact emerges, namely, that as many women with breech presentation go into labour spontaneously at the 38th week as are, in fact, induced. The rest are accounted for by multiple pregnancy and gross prematurity. In primiparæ the average length of labour in induced cases was nineteen and a half hours and in non-induced cases twenty-four hours. The Løvset manœuvre is always used for extracting the arms. The corrected fœtal mortality in induced cases is 5·5% and in non-induced cases 8·4%. Cæsarean section has been employed five times in 226 cases in ten years.

My main indications for Cæsarean section are Rhesus-negative primiparæ; cases referred in, at or over time with big babies; elderly primiparæ who have an unpropitious labour after induction.

In an attempt to assess the state of the baby when it is born as far as the shoulders, the fœtal pulse-rate has been counted by auscultation over the heart. Graphs have been drawn which show that the rate falls to 80 and is maintained at that speed for up to fifteen minutes. I do not advocate waiting as long as this, but submit that a reasonable interval should be allowed to elapse before resorting to extraction in order to give the head time to come slowly through the pelvis. If episiotomy is necessary it should be in the mid-line.

**Mr. Gilbert Dalley** said that external cephalic version was preferable to breech delivery, especially for the occasional or less experienced obstetrician. The tempo of version was all-important.

He showed tables illustrating a series of booked confinements in the West Hill Hospital, Dartford, for the ten years, 1947–1956: there were 10,938 deliveries, of which 109 were delivered as a breech *per vaginam*. The corrected perinatal mortality for the breech deliveries was 6·3%, compared with the overall gross perinatal mortality of 2·9%. 572 external cephalic versions were performed of which 498 (87%) were successful. An anæsthetic was only used in 33 cases, successfully in primigravidæ thirteen times and in multigravidæ once, and unsuccessfully in primigravidæ eighteen times and multigravidæ, once.

Analysis of the versions according to the stage of pregnancy showed that those performed by the 35th week were successful in 91% of primigravidæ and 94% of multigravidæ, whereas from the 36th week the percentage of success dropped to 58% in primigravidæ and 79% in multigravidæ.

Versions should be done before the 35th week, in which case no anæsthetic should be necessary.

**Mr. J. S. Hesketh** said he had always been taught to avoid traction in breech deliveries and was rather concerned at the amount of traction necessary in Mr. Hamilton's method not only to deliver the arms but also particularly to deliver the head.

He wished to seek Mr. Hamilton's reassurance that in Burns' and Marshall's original papers they stated that in the delivery of the head the obstetrician should use one hand to exert traction on the legs and the other to exert any suprapubic pressure that was required.

He had always understood that by this means no undue traction could be employed and the danger of excessive traction avoided.

**Mr. Wilfrid G. Mills** said he wished to emphasize some points that had not already been given proper weight. Breech deliveries should be clearly divided into two varieties. The extended breech was an excellent presenting part, it fitted the cervix well, it allowed an easy first stage with good dilatation of the cervix and no risk of prolapse of the cord. On the other hand the flexed breech was a worse presentation with late engagement, poor dilatation after slow descent, premature rupture of membranes and frequent prolapse of cord. The former was typical of the primigravida and the latter of the multiparous patient.

He strongly subscribed to the performance of external version. He was uncertain why the opening speakers had suggested that it should be attempted at the 32nd week. He believed it should be performed whenever a breech presentation was diagnosed, provided that no particular difficulty was encountered. It might well be impossible in cases of unicornuate uterus, even at a very early stage of pregnancy.

In labour he believed that there was a place for a modified trial of labour in patients with a slight degree of pelvic contraction: a delay of over twenty-four hours before full dilatation would usually indicate a degree of mechanical obstruction to the descending breech that foreshadowed dystocia for the head, and such cases were better delivered by section. He believed that the passage of meconium in the first stage of a breech labour was indeed a sign of fœtal distress, due perhaps to compression of the fœtal end of the umbilical cord as the breech descended into the pelvic cavity.

It was generally recognized that intracranial hæmorrhage was liable to occur in the after-coming head with considerably less trauma than was necessary in cephalic presentations: the conventional explanation was that the after-coming head of the breech required extra time to allow for moulding during its passage through the pelvis. He believed that this was a misconception and that the liability to fatal hæmorrhage was due to the after-coming head being congested with all the fœtal venous blood that had been forced up during the delivery of the lower limbs through the tight vulval ring. The life-saving delay in delivery of the head acted by allowing this venous congestion to disperse as the blood flowed back into the fœtal lower extremities. The right procedure was in fact adopted for the wrong reasons.

**Dr. J. Vincent O'Sullivan** said he would like to support Mr. John Peel most strongly in his plea for external version in breech cases during the antenatal period. He, too, was sure that the breech should be turned somewhere between the 30th and the 34th week. In his hospitals the incidence of breech deliveries was 1%. If it had not been turned by the 34th week the patient should be admitted to hospital and given either heavy sedation or a general anæsthetic, including ether if necessary, to do a version.

He always took an X-ray before attempting version under anæsthetic so that he could be certain of the position of the baby.

He usually succeeded in turning the breech by making the buttocks follow the head; rarely had he been able to do it the reverse way as suggested by Mr. Peel.

A trial of labour with a breech was quite possible if the breech did not reach the perineum, when it was wiser to do a Cæsarean section. Unlike Mr. Hamilton, when he had applied forceps to the after-coming head, he straddled the baby over his right forearm and gently pulled and "rolled" the head out over the perineum, making sure that the nape of the neck was pressed close against the symphysis pubis, the Mauriceau-Smellie-Veit manœuvre with forceps.

**Mr. John Hamilton,** in reply, pointed out that he did perform external version but not under anæsthesia.

He agreed with Mr. Vartan about the place of induction of labour before term in breech presentation.

Dr. Hesketh had queried the amount of traction used in the Burns-Marshall method. It was important to keep steady traction in order to keep the head in a state of flexion.

Mr. Mills made many points to most of which he would agree. He especially agreed to the differentiation between extended breech in the primigravida and flexed breech in the multipara. He would also agree to the trial of labour in breech delivery although he preferred to call it trial breech delivery. He could not, however, agree to his view that the value of the baby hanging down is to drain blood from the brain more especially when he had earlier said that the infant was deprived of blood owing to compresson of the cord.

Dr. O'Sullivan questioned lifting up the infant before putting the forceps on to the after-coming head. The reason for this was that with the infant held up it was possible to get air into the vagina and thus allow more time for delivery. It was also an excellent way of draining the air passages of mucus.

[*January* 24, 1958]

THE following cases and specimens were shown:

**Vaginal Deposits of Renal Carcinoma.**—Dr. H. P. FERREIRA.

**Juvenile Streptococcal Vaginitis.**—Mr. WILFRID MILLS.

**Postmenopausal Bleeding Due to Fibrosarcoma of the Vagina.**—Dr. J. D. BAEYERTZ.

**Two Cases of Carcinoma of the Fallopian Tube.**—Miss JOCELYN MOORE.

**Ectopic Pregnancy in a Tuberculous Tube.**—Mr. C. W. TAYLOR.

**Pregnancy and Endometriosis following Perforation of the Uterus.**—Dr. E. M. EDWARDS.

**Pregnancy Complicated by a Retro-peritoneal Tumour of Possible Mesonephric Origin.**—Dr. J. K. MORRISON.

**Intra-uterine Amputation of Fœtal Limbs.**—Dr. H. G. KOHLER.

**Severe Accidental Hæmorrhage with No Evidence of a Fibrinogenæmia, Treated by Blood Transfusion and Cæsarean Hysterectomy.**—Dr. D. N. STRUAN ROBERTSON.

# Section of Dermatology

President—JOHN T. INGRAM, M.D., F.R.C.P.

[*October* 17, 1957]

**Chronic Granuloma of Face.**—F. F. HELLIER, O.B.E., F.R.C.P.

A. D. D., male, aged 35.

*History.*—Three years' history of ulceration of face, said to have started following squeezing a blackhead. The condition has steadily spread despite all forms of treatment and he now has five separate lesions.

Individual lesions start as a pustule surrounded by an inflamed area. This gradually breaks down and forms an indolent inflammatory patch with ulceration which slowly spreads despite treatment. There is no history of taking bromide.

*Present state.*—There are five lesions, three on the left cheek, one on the forehead and one on the right cheek; the largest, on the left cheek, is roughly triangular, about 2 × 1½ in.; the most recent one, about three weeks old, is a little pustule surrounded by redness in front of the left ear. The largest lesion is fairly well defined, scarred, centrally depressed and crusted; it oozes a few beads of pus when pressed (Fig. 1).



FIG. 1.

*Investigations.*—W.R. negative. X-ray chest normal. Sinuses normal. Serum proteins normal. Blood count normal. B.S.R. 13 mm. in one hour. Bacteriology: Usually *Staphylococcus aureus*, sometimes sterile, once coliforms. Mantoux positive 1/1,000. Histology (several occasions): A chronic granulomatous lesion in dermis and subcutaneous tissue with small irregular areas of necrosis. There are numerous giant cells, but no typical tuberculous follicles. No tubercle bacilli found. Examination for blastomycosis negative.

*Treatment.*—A wide range of local antiseptics and antibiotics. Internally: Antibiotics, sulphonamides, iodides, steroids, calciferol, &c. X-rays have seemed to help a little but not permanently. Curetting the lesions was followed by temporary healing but after varying periods they all relapsed.

In this case the question to be answered is whether the fault lies in the soil or the seed. We have never found anything but banal organisms and I feel that this must be considered a peculiar reaction on the part of the patient. There is no evidence of what causes the peculiarity, he shows no signs of any general abnormality—his serum proteins are normal, he has no symptoms of colitis, &c. I have seen similar lesions occasionally on arms or legs and have labelled them "dermatitis vegetans". In one case curetting extensive areas on the legs led to healing, but years later the condition broke out on the arms. This man has proved resistant to all forms of treatment including curetting.

**Chloracne.**—C. M. RIDLEY, M.R.C.P.

G. M., male, aged 32. Chemical worker.

*History.*—This man has had a rash, which began on the face, since November 1956. He has felt generally ill for a few weeks.

The rash began about two months after he started work in a chemical factory. It did not clear when he was away from the factory for three months. He handles various chemicals, including dichlorphenol and trichlorphenol; he wears protective clothing and is splashed with the liquid only occasionally on the arms.

Five other men are said to have been affected in the same way for the same period of time. The others had all worked there for several months before this patient arrived.

*Treatment.—At work:* Ultra-violet irradiation and injections (? vitamin $B_{12}$). Two weeks before first attendance at hospital—bromide mixture. Since attending hospital—methionine.

*Previous history.*—No acne.

*Family history.*—No skin disease.

*On examination.—Skin:* face, external auditory meatus, back, chest, shoulders, buttocks, scrotum and to a lesser extent on the forearms: florid eruption of densely packed comedones, papules and pustules. Pigmentation of U.V.R. on back.

*Other systems* normal.

*Investigations.*—Chest X-ray normal. ESR 5 mm. in one hour (Westergren). Hb 96%; white cells 12,000 (polys. 62%, lymphos. 33%, monos. 3%). Bilirubin: 0·1 mg.%. Empirical liver function tests normal. Plasma proteins: 7·4%; albumin 4·8, globulin 2·6 grams%.

*Comment.*—The chloracne was presumably caused by dichlorphenol and trichlorphenol; no higher chlorinated phenols, other organic chlorine-containing compounds, tars or oils are handled. These compounds seem rarely to cause chloracne, but Dugois and Colomb reported a similar outbreak in 1956 in a French factory.

Probably the systemic disturbances are due to absorption, but whether the acne is brought about in the same way is still debated; that this is the case is suggested by the fact that new lesions may appear long after exposure has ceased.

REFERENCE

DUGOIS, P., and COLOMB, L. (1956) *Lyon méd.*, **196**, 446.

**Dr. H. R. Vickers:** I have seen several of these cases occurring in electricians and in workers in the chromium plating industry in which these chlorinated waxes are used. The large number of comedones are characteristic and there is an extremely slow response to treatment.

**Dr. G. A. Hodgson:** This is an odd case because the areas most involved are those which are covered by clothing when the patient is doing his job. Chloracne is usually produced by skin contact, but probably absorption can occur. Cases have been described in connexion with the manufacture of D.D.T. (Bowen, S. S., and Moursand, M. P., 1957, *Arch. Derm. Syph., Chicago*, **75**, 743) which is a chlorinated hydrocarbon product and in those cases it was suggested that in the production chlorinated compounds are formed in the process from hydrocarbons which are mixed with the other chemicals. An article by Shelley and Kligman (1957) suggests that once the chlorinated naphthalenes are no longer applied, the condition continues to erupt for some months and then eventually resolves after very many months with scarring and acne conglobata-like lesions. The article deals with the experimental production of chloracne with penta and hexachlornaphthalene (Shelley, W. B., and Kligman, A. M., 1957, *Arch. Derm. Syph., Chicago*, **75**, 689). It explained how eventually the whole of the sebaceous apparatus is turned into a keratin-producing machine. In fact, the whole sebaceous gland may disappear, but it does recover.

**Dr. R. D. Sweet:** Some four or five years ago Dr. F. A. Whitlock experienced a small outbreak of cases in Falmouth, which resulted from exposure to unknown chemicals when a ship which was carrying chemicals at Falmouth caught fire. No one knows what was produced by the combustion, but within a few weeks three or four members of the crew developed quite dramatic eruptions with large horny cysts over most of their bodies. They were all involved in fighting the fire and presumably came into brief contact with the fumes. Parallel with this case, there may have been more absorption systemically than there was contact with the skin.

**Dr. F. F. Hellier:** Workers who handle chlornaphthalene may develop general toxic symptoms such as liver damage, or local skin lesions. The former occur when the chlornaphthalene is volatilized during its actual manufacture whereas the latter occurs in the cold and is more probably a local contact phenomenon. This man has got his rash in areas beyond those of immediate contact, but it may be that chlorphenol is more volatile than chlornaphthalene and this would account for its wider distribution.

I would like to refer to the cases which Dr. Hodgson mentioned, produced artificially by Kligman

several of whom I saw last year in Philadelphia. Some patients developed very formidable lesions, spreading widely on the scalp and lasting for many months after the last application of the irritant. Admittedly these men were negroes in whom the sebaceous system is well developed, but it does seem as if some process had been set going often by only a brief exposure, which then became self-perpetuating. Kligman's work (Shelley, W. B., and Kligman, A. M., 1957, *Arch. Derm. Syph. Chicago*, **75**, 689) does show that the rash is due to local contact and not secondary to internal absorption.

**Dr. J. E. M. Wigley:** I think I brought some of the first cases of chloracne shown at this Section, during the war, and they mostly occurred in young women who were occupied in dipping parts in molten See-kay wax used for the insulation of deep sea cables (Wigley, J. E. M., 1944, *Brit. J. Derm.*, **56**, 230). There was very much less evidence of ordinary acne in those cases. The parts chiefly affected were the hair margin, the forehead, the cheeks and the lobes of the ears. Many of the lesions were cystic (resembling sebaceous cysts). The people I saw were working in a very primitive sort of factory with something like an old cauldron in which stuff was melted, and with a very inefficient dust and fume extractor. They said there was a very strong smell of chlorine throughout the whole place. The nurse who was sent there to run a small first-aid station had her department about 25 yards from the cauldron. There was no direct contact and yet within a few months she developed typical lesions, which were much more cystic than those we have seen to-day. Whether the condition is exactly the same as in this case I am not prepared to say, but we came to the conclusion it was probably due to the inhalation of or contact with the chlorine part of the vapour.

**Dr. J. S. Pegum:** In view of what Dr. Hodgson has said about the similarity of these compounds to D.D.T., I wonder whether the body treats them in the same way and when they are absorbed (if they are absorbed) they are not laid down in the fat and then slowly released. If this is so it might also account for the localization in the sebaceous glands.

**Dr. G. C. Wells:** I do not think that D.D.T. itself produces chloracne; it is surely the chlorobenzene used in its manufacture which does so.

**Dr. C. D. Calnan:** One of the points that Kligman mentioned was that the patients may get worse after contact with the substance has stopped. It is suggested that absorption may be responsible for that and for the dissemination, but I do not think this is true. Kligman favoured the explanation that the substance was spread over the skin surface; he found experimentally that if you painted a small square of skin it was spread by the clothing.

He has also dealt with the histology of chloracne in detail; this substance apparently has the power of changing sebaceous cells into keratinizing cells. I think we have something of tremendous importance to study here.

The following cases were also shown:

**Incontinentia Pigmenti.**—Dr. R. G. HOWELL (for Dr. R. T. BRAIN).

(1) **Oral Epithelial Nævus.** (2) **Hansen's Disease.**—Dr. C. M. RIDLEY.

**? Tertiary Lues.**—Dr. P. A. J. SMITH.

**Kaposi's Idiopathic Hæmorrhagic Sarcoma.**—Dr. G. C. WELLS.

**Acne Agminata.**—Dr. E. WILSON-JONES (for Dr. G. C. WELLS).

[*November* 21, 1957]

**Mucous Membrane Pemphigoid.**—J. H. ALLISON, M.R.C.P. (for F. RAY BETTLEY, F.R.C.P.).

Mrs. C. E., aged 73.

*History.*—For about two years she has had recurrent blisters on the scalp, and for the last ten months lesions have occurred on the skin in the region of the umbilicus. The appearance of the blisters is preceded by reddening of the skin and itching. The blisters on the scalp are followed by scarring and alopecia, and those on the peri-umbilical skin by scarring and pigmentation. Occasionally lesions have occurred over the shoulders and beneath the right breast. No blisters have occurred on the eyes or in the mouth.

*On examination.*—At various times flaccid blisters of variable size around the umbilicus arising on reddened skin have appeared. The blisters on the scalp have tended to be small, up to 0·5 cm. in diameter, chiefly affecting the vertex and frontal region. The affected areas subsequently show white papyraceous scarring.

*Histology* from a lesion in the umbilical region shows a subepidermal bulla. No evidence of acantholysis. There is inflammatory cell infiltration in the underlying dermis with some early fibrosis.

*Discussion.*—This case is shown simply to emphasize once again that "ocular pemphigus" can be diagnosed before any lesions occur on the eyes or the mucous membranes.

The diagnosis rests on the appearance, in one or a few localized areas, of a recurrent subepidermal bullous eruption, going on to scarring.

Skin involvement appears to develop in about a third to a half of all cases of this disease. 9 out of Lever's 19 cases (1944) and 2 of Church and Sneddon's 7 cases (1953) showed skin lesions. Lever's series showed intervals varying from twenty-two months to seven years between the onset of the skin eruption and the development of mucosal blisters, in cases in which the skin had been affected first.

The blisters on the skin occur almost always in one or a few localized areas. However, in one of Lever's cases the skin lesions were generalized.

REFERENCES

CHURCH, R. E., and SNEDDON, I. B. (1953) *Brit. J. Derm.*, **65**, 235.
LEVER, W. F. (1944) *Arch. Derm. Syph., Chicago*, **49**, 113.

**Pemphigus Vegetans.**—F. RAY BETTLEY, F.R.C.P.

This man of 52 first developed erosions of the mouth mucosa in 1953. The diagnosis of pemphigus was made at that time by Dr. H. Haber, who found acantholytic cells in scrapings. Since that time he has been treated with cortisone, ACTH and, more recently, prednisone.

In August 1957 he developed his first skin lesion: a group of blisters appeared on the front of the chest. Biopsy of these showed a typical lesion of pemphigus vulgaris. In the last two or three weeks, fresh lesions have appeared on the front of the chest, in the axillæ and in the right groin. Those in the axillæ have started to vegetate.

His present dose of prednisone is 40 mg. a day and this is evidently not controlling the eruption.

**Dr. F. Ray Bettley:** I saw this patient's vegetating lesions for the first time to-day and thought it was particularly interesting to see them at this extremely early stage.

There are two particular points about this case. One is the very long time—four years at least—between the onset of the condition in the mouth and the first skin lesion. The second point is that he seems to have escaped from control on a dose of 40 mg. prednisone. I have had no experience of treating pemphigus vegetans with steroids and that is one of my reasons for bringing the case forward now, so that I may have the benefit of members' comments.

**Dr. I. B. Sneddon:** I entirely agree with the diagnosis of mucous membrane pemphigus even though the mucous membranes are not involved. I thought the scarring on the scalp was very characteristic. I know of one case with lesions on the scalp which for twenty years were diagnosed as lupus erythematosus before they were correctly diagnosed as the lesions of mucous membrane pemphigus. No other variety of pemphigus produces scarring to this extent.

**Dr. C. H. Whittle:** Are these cases of mucous membrane pemphigoid expected to respond to steroids? In answer to Dr. Bettley's question as regards the response of pemphigus vegetans cases to steroids, we have one man, a farm labourer, who has been under control for five years and is completely controlled by very small doses—25 mg. cortisone daily—and is doing a full day's work. He was at point of death before his disease was controlled and spent nearly a year in the wards.

**Dr. E. W. Prosser Thomas:** I have a similar case at present. He could not be controlled with less than 70 mg. prednisone. He gradually improved, the dose was reduced and now it is about 20 mg. per day. He has been back at work for some months and is practically free of lesions.

**Dr. R. E. Church:** In reply to Dr. Whittle's question about the control of ocular pemphigus: in my experience one can control the skin lesions fairly easily on small doses of prednisolone but, however high the dose given, although one can obtain slight subjective improvement in the mucosal lesions, one can never induce them to heal.

**Dr. Eric Waddington:** The response to treatment with steroids may depend on the clinical variety of pemphigus vegetans. We have two patients, one of whom developed widespread bullæ on the back and many months later vegetations occurred in the flexures. She is only controlled with high dosage of prednisone, as for example in pemphigus vulgaris. The second patient has never had widespread bullæ. The lesions have always consisted of vegetations restricted to the flexures and muco-cutaneous junctions. She has completely cleared with small dosage of prednisone.

I agree that steroid therapy in benign mucous membrane pemphigoid is disappointing. In three of my patients the skin and oral lesions have been arrested but there has been no change in the ocular lesions.

(*To be continued*)

# Clinical Section

President—E. W. RICHES, M.C., M.S., F.R.C.S.

[*November* 8, 1957]

**Gummatous Ulcers with Gross Hepatomegaly and Anæmia.**—A. B. WOOTLIFF, M.B., Ch.B. (for J. M. MILLOY, F.R.C.S.).

Married woman, aged 58, caretaker.

Admitted to St. Mary Abbots Hospital on 14.10.57 with a diagnosis of "varicose ulcers of the leg".

*History.*—For one year increasing malaise and for eight weeks superficial ulceration of the left leg above the lateral malleolus. One month before admission she developed a swelling below the middle of the left clavicle which broke down forming a deep punched-out discharging ulcer. Two hæmorrhages from the leg ulcer had occurred. There was no history of alcoholism or of syphilis.

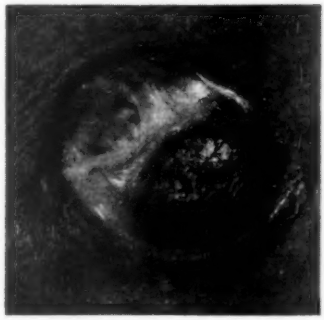


FIG. 1.—Ulcer below the left clavicle.

*On examination.*—No evidence of varicose veins or vascular disease; superficial shelving-edged ulcer on left ankle. Ulcer beneath left clavicle with serpiginous indurated edges (Fig. 1). Both ulcers were secondarily infected. The only nervous involvement was a sensory loss of stocking distribution on the left leg. Marked onychogryphosis. Abdominal examination revealed gross hepatomegaly with distended superficial abdominal veins. There was moderate sacral and ankle œdema.

*Investigations.*—Blood: W.R. and Kahn positive. Stools: occult blood negative. Liver function tests: bilirubin 0·6 mg.%: thymol turbidity 3 units: alkaline phosphatase 2·4 units: Hb 4·3 grams%: R.B.C. 2,800,000: P.C.V. 18%: M.C.V. 64 cu.$\mu$: M.C.H. 15 $\mu\mu$g: M.C.H.C. 24%: nucleated red cells 1: marked aniso- and poikilocytosis. Microcytosis +. Serum iron 23 $\mu$g.%.

15.1.58: Treated vigorously with penicillin, blood transfusions and chiropody with striking improvement. The ulcers have completely healed and the patient is ambulant, but the liver is still very enlarged.

**Addison's Disease with Glycyrrhizophilia.**—J. P. KNOWLES, M.B., B.Chir., D.Obst. (for RICHARD ASHER, M.D., F.R.C.P.).

H. L., male, aged 36.

July 23, 1957: Admitted to the Central Middlesex Hospital for investigation of suspected Addison's disease.

*History.*—Eleven years ago he had pulmonary tuberculosis, and was treated with artificial pneumothorax for five years. The disease has been inactive since.

Eighteen months ago: Patches of oral pigmentation noticed by dentist. In very good health at the time so they were presumed to be racial (Italian father and Caucasian mother).

For nine months: Weakness, fatigue and early morning dizziness.

For three months: Loss of weight (about 3 kg.), and, according to his family doctor, increasing pigmentation. (Patient and his wife denied this and put it down to a recent Mediterranean holiday.)

He admitted to no gastro-intestinal symptoms whatever.

*Clinical examination.*—Rather dark-skinned, weak, anxious man. Nipples, vaccination scar and buccal mucosa deeply pigmented. Black freckles on the back.

B.P. 110/80 lying; 100/80 standing.

*Investigations.*—Serum sodium 127·5 mEq./l., serum potassium 5·4 mEq./l., blood urea 44 mg./100 ml. Absolute eosinophil count (average of six counts) 31/c.mm. (range 19–71/c.mm.) Failed to excrete a water load.

*Progress.*—During the course of an ACTH stimulation test (Nabarro, 1954) he went into adrenal crisis. (Serum sodium 95 mEq./l., serum potassium 6·5 mEq./l., blood urea 66 mg./100 ml.) Fortunately, he responded promptly to intravenous saline and hydrocortisone and has since remained well on maintenance salt and cortisone.

Urine 17-ketosteroids (estimated after the crisis on urine collected during ACTH test) 4·6 mg./twenty-four hours (average of four days).

*Comment.*—This case was diagnosed late because: (*a*) The significance of the pigmentation was dubious and a fear of recurrence of tuberculosis seemed to explain his anxiety. (*b*) But most confusing was his denial of gastro-intestinal symptoms, which are "almost a *sine qua non* of Addison's disease" (Selye, 1949). However, after the crisis he admitted having lost his appetite for everything other than salt and liquorice sweets. For three months he had been eating up to 0·25 kg. of very salty black olives and a similar quantity of liquorice sweets daily.

Salt-craving is a well-known symptom of Addison's disease and occurred in 16% of 66 patients described by Thorne *et al.* (1942). Liquorice-craving (for which Dr. Asher has suggested the name glycyrrhizophilia) has not been described before. It is well established that liquorice has a desoxycorticosterone-like action (Molhuysen *et al.*, 1950) and it has been successfully used in the treatment of some cases of Addison's disease (Groen *et al.*, 1951; Borst *et al.*, 1953).

0·25 kg. of liquorice sweets contain about 6 grams of extract of liquorice (personal communication from Geo. Bassett & Co. Ltd., Sheffield). Cases of Addison's disease have been maintained on 3 grams to 60 grams of liquorice extract per day, the smaller quantity being sufficient when the disease was controlled.

It seems reasonable to assume that the salt and liquorice both helped in the suppression of symptoms, and that when their consumption ceased after admission to hospital this precipitated the adrenal crisis.

A preliminary, retrospective survey amongst other known cases of Addison's disease suggests liquorice-craving is at least as common a symptom as salt-craving and that either, or both, occur with sufficient frequency (about 25%) to make it well worth while asking about them specifically in any case of suspected Addison's disease.

## REFERENCES

BORST, J. G. G., TEN HOLT, S. P., DE VRIES, L. A., and MOLHUYSEN, J. A. (1953) *Lancet*, i, 657.

GROEN, J., PELSER, H. E., WILLEBRANDS, A. F., and KAMMINGA, C. E. (1951) *New Engl. J. Med.*, **244**, 471.

MOLHUYSEN, J. A., GERBRANDY, J., DE VRIES, L. A., DE JONG, J. C., LENSTRA, J. B., TURNER, K. V., and BORST, J. G. G. (1950) *Lancet*, ii, 381.

NABARRO, J. D. N. (1954) *Lancet*, ii, 1101.

SELYE, H. (1949) Textbook of Endocrinology. Montreal.

THORNE, G. W., DORRANCE, S. S., and DAY, E. (1942) *Ann. intern. Med.*, **16**, 1053.

[*December* 13, 1957]

**Pulseless Disease and Pulmonary Sarcoidosis.**—T. M. CHALMERS, M.D.

*Pulseless disease* (*Takayashu's disease*).—Pulseless disease is a syndrome caused by a progressive obliterating arteritis of the arteries to the head and neck with a compensatory development of collateral circulation. It occurs mostly in Japan where it was first described in 1908 by Takayashu (1908) and it principally affects young women. It is one of a group of diseases characterized by obstruction of the great vessels arising from the aortic arch—a group named as The Aortic Arch Syndrome by Frøvig (1946).

Clinically there is progressive ischæmia of the upper half of the body. The arms become easily fatigued, the pulses cannot be felt nor the blood pressure measured.

There may be ischæmic atrophy of the gums and the skin of the face, and because of the cerebral ischæmia strokes, faints, fits and psychic changes are common. In Japan the illness is called Takayashu's disease. Takayashu stressed the eye changes: there is often degeneration of the iris and retina or opacities in the lens or cornea; retinoscopy may reveal micro-aneurysms and hæmorrhages, the veins may be "beaded" by numerous constrictions with the venous flow noticeably slow.

Apart from the ischæmic symptoms there may be cardiac hypertrophy with hypertension of the lower limbs. The frequent occurrence of fever, tachycardia and a high sedimentation rate suggests a relationship to rheumatic or other infections but the essential cause of this illness is purely conjectural and the treatment no more than palliative.

*Case History*

Miss M. C., aged 30, school teacher.

February 1957: Clinical examination and fluoroscopy (in Madrid) said to be normal.

*History.*—April–July 1957: After working for three weeks in London as a hospital cleaner she developed painful nocturnal tingling in the hands and forearms, which subsided within a few weeks.

*Examination.*—Both radial pulses absent, brachial pulses grossly diminished. Right scalene lymph node enlarged. B.P. in arms not recordable. B.P. (popliteal) 150/70. No other significant clinical findings.

*Investigations.*—E.S.R. 30 mm. in one hour (Westergren). Blood W.R. negative. Mantoux 1:1,000 positive. Chest X-ray: bilateral hilar enlargement with widespread mottling in both lung fields. Lymph-node biopsy: sarcoid tissue.

November 1957: After treatment with prednisone 5 mg. t.d.s. for six weeks felt less tired and slight effort dyspnœa had disappeared. Chest X-ray showed considerable resolution. Arm pulses still markedly diminished. Angiocardiography revealed narrowing of the left common carotid as well as of both subclavian arteries.

She is thought to be an example of the pulseless disease (Takayashu's disease) with incidental and unrelated sarcoidosis. An excellent account of this form of arteritis is given by Ask-Upmark (1954; Ask-Upmark and Fajers, 1956).

REFERENCES

ASK-UPMARK, E. (1954) *Acta med. scand.*, **149**, 161.
—— and FAJERS, C.-M. (1956) *Acta med. scand.*, **155**, 275.
FRØVIG, A. G. (1946) *Acta psychiat. Kbh.*, suppl. 39.
TAKAYASHU, M. (1908) *Acta Soc. ophthal. jap.*, **12**, 554.

**Traumatic Aneurysm of the Popliteal Artery in a Boy Aged 11 Years, Associated with an Osteoma of the Lower Femur. Treatment by Aneurysmectomy and Repair of Vessel Wall.**—A. M. DESMOND, F.R.C.S.

Traumatic aneurysms of the popliteal artery in children occur in modern civil practice only rarely. In the days of stage-coaches, post boys were said to develop such aneurysms from sitting on a wooden seat on bumpy roads. Usually the trauma causing the aneurysm is relatively mild. The artery is most vulnerable at the adductor opening where it is liable to be compressed against the lower femoral shaft. In this case quite minor trauma caused a small tear of the vessel because there was an osteoma at this site. Two weeks passed before the resulting false aneurysm became pulsatile and repair of the vessel with excision of the aneurysmal sac was carried out without technical difficulty.

The child had always walked slightly stiffly with his left leg.

*History.*—8.10.57: Attended casualty department, St. James' Hospital.

Twelve days ago he received a kick on the back of his left knee at football and a swelling had since developed.

***Examination*** revealed a diffuse swelling of the back of the knee which was diagnosed as a hæmatoma. No pulsation was noticed by the casualty officer. The knee was bandaged and the child sent home.

15.10.57: Attended again with pain and no diminution in size of swelling. X-ray revealed an osteoma of the lower end of femur (Fig. 1). Seen by the orthopædic surgeon who continued supportive treatment.



FIG. 1.—Showing osteoma of the lower end of femur.



FIG. 2.—Arteriogram of the aneurysm.



FIG. 3.—Post-operative arteriogram showing normal vessel continuity.

28.10.57: Attended again and now the swelling was noticed to be pulsatile and he was referred to the Vascular Clinic, St. James' Hospital. On admission he was found to have a large pulsatile swelling behind the left knee. The distal pulses were normal. A femoral arteriogram showed an aneurysm of the popliteal artery with a small break in the continuity of the artery in the centre of the aneurysmal shadow (Fig. 2).

30.10.57: An incision was made on the medial side of the popliteal fossa. The femoral artery was controlled at the lower end of Hunter's canal. The adductor magnus tendon was divided and an aneurysm the size of a tennis ball was found. The popliteal artery was controlled below it. The aneurysm was dissected out and found to communicate by a small hole in the artery. Opposite this hole was a small osteoma. The aneurysm was removed piece-meal and the osteoma chiselled off. The small hole in the popliteal artery was sutured and arterial continuity re-established. The distal pulses were normal at the end of the operation and have remained so.

A post-operative arteriogram showed normal vessel continuity (Fig. 3).

**Ectopic Phæochromocytoma.**—R. E. WILLIAMS, M.R.C.P. (for Professor M. L. ROSENHEIM, C.B.E., F.R.C.P., B. J. HARRIES, F.R.C.S., and JOHN LISTER, M.D.).

Phæochromocytomata occur in the adrenal medulla, but may occur in any chromaffin deposit, e.g. the carotid body, or in the organ of Zuckerkandl on the aorta between the mesenteric artery and the bifurcation. More than half the cases affect patients between 20 and 50 years of age, but one has occurred as early as 16 months. The sexes are almost equally affected. About 10% of cases are bilateral, 10% are extra-adrenal but lying not far from the gland and 10% are malignant (Aird, 1957).

There is occasionally a familial incidence in unilateral cases and familial occurrence with other endocrine disorders such as thyrotoxicosis has been noted.

The active secretion of the normal adrenal medulla is 80% adrenaline. The secretion from a phæochromocytoma, on the other hand, contains a high proportion of nor-adrenaline which has a much greater vasoconstrictor effect and raises both systolic and diastolic pressure, unlike adrenaline. The clinical picture is usually characteristic, and the diagnosis should be suspected on clinical grounds.

A sustained or intermittent hypertension may be produced by this tumour and the size of the tumour may occasionally be detectable clinically either by the presence of a palpable mass or a displaced kidney. The confirmation of the diagnosis rests on biochemical tests. The provocative test with intravenous histamine, in doses ranging from 0·015 mg. to 0·05 m[illegible]

is now rarely used, although this test is carried out in some centres for patients whose resting blood pressure is less than 170/110 (Sprague *et al.*, 1953). Intravenous phentolamine (Rogitine test) has been held to be a safe procedure (Helps *et al.*, 1955). In many centres where assay of pressor amines is available, it is no longer used because the sudden fall of blood pressure that constitutes a positive result may be dangerous. Pressor amines in the urine give virtual proof of the diagnosis and the test carries no risk. Unfortunately the estimation is difficult, and can be carried out only in special centres. Finally, the tumour may be localized radiologically by plain films or tomography, and perirenal insufflation with $CO_2$ or oxygen may also demonstrate a mass.

The removal of these tumours requires the most careful co-operation between surgeons, physicians and anæsthetists. Post-operative care also requires the most careful regulation of the blood pressure and a nor-adrenaline drip is usually required for about the first twenty-four hours.

*Case Report:*

Mrs. G. W. A., aged 40.

9.5.57: Admitted to hospital as a case of hypertensive encephalopathy with headache and vomiting.

*Previous history.*—Eight years ago began having attacks of palpitations and sweating followed by occipital headache and a feeling of weakness. Found to be hypertensive and thought to have chronic pyelonephritis. During the last two years the attacks had begun to occur almost daily, and the headaches had become more severe and were accompanied by vomiting.

*On examination.*—C.N.S.: Blurring of disc margins, tortuous arteries and arterio-venous nipping. Bilateral exudates with 2 flame-shaped hæmorrhages on the left. B.P. 235/160. Femoral pulses present. Apex beat in anterior axillary line, heaving triple rhythm present.

*Investigations.*—Blood urea: 25 mg.%. C.S.U.: Faint cloud of protein. Occasional hyaline casts and very occasional polymorphs and red cells. Culture sterile. Concentration and dilution test: concentrated to 1020.

ECG: Sinus rhythm. Left ventricular hypertrophy and strain. Heart X-ray: slight cardiac enlargement. Lung fields normal. I.V.P. normal.

Rogitine (phentolamine) test: Very strongly positive. Her blood pressure fell from 250/150 to 90/40 in three and a half minutes and at one stage her B.P. was unrecordable. She became deeply unconscious and on recovery from this had a nominal aphasia and was completely disorientated. She fully recovered in three days.

Urinary pressor amines: Gross excess present equivalent to approximately 400 mg./twenty four hours; mostly nor-adrenaline.



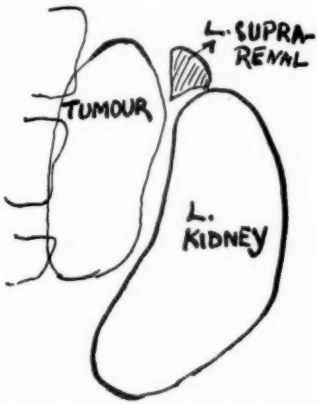



FIG. 1.—Showing a large round mass 4 in. long by 2½ in. broad lying in front of and to the medial side of the left kidney. It is in the position of the calcified region, visible in the plain films, although little or no calcification is visible in the tomographic cuts. The left suprarenal is clearly demonstrated to be separate from the mass and normal in size.

Perirenal air insufflation and tomography: Large mass in front of and medial to the upper half of the left kidney. Left suprarenal shown to be separate from the mass and normal in size. Appearances considered consistent with an ectopic phæochromocytoma.

*Operation* 29.7.57 (Mr. Bernard Harries).—Left upper paramedian incision extending as a "Y" into left costal margin. An ectopic phæochromocytoma bulging into the lesser sac and densely attached to all neighbouring structures especially to pancreas, splenic artery, cœliac axis and aorta, was removed. A large venous channel drained the tumour into the left renal vein. The left adrenal gland was normal. Right adrenal and kidney felt normal. Biopsy of left kidney taken. Operation lasted five hours. The patient was digitalized before operation. During induction the blood pressure rose to 300/190 and phentolamine 2·5 mg. was given to control this. After ligating venous drainage of the tumour nor-adrenaline was required to maintain the blood pressure, the lowest recorded pressure being 95/75.

*Post-operative progress.*—Eight hours post-operatively was found to have left hemiparesis and did not fully regain consciousness for seventy-two hours. Nor-adrenaline drip was maintained for twenty-eight hours post-operatively, a total of 30 mg. of nor-adrenaline being given.

*Subsequent progress.*—Almost complete recovery of left hemiparesis. Blood pressure 160/110. No palpitations, no sweating and no headaches. Fundi show marked regression of changes. Urinary pressor amines within normal limits.

*Histology of tumour* (weighing 76 grams).—Benign phæochromocytoma.

*Discussion.*—This report demonstrates that the diagnosis should be suspected on the clinical history; the patient described characteristic episodic attacks over a period of years. The diagnosis was virtually confirmed by the result of the phentolamine test, and the alarming sequelæ of the test emphasize its potential dangers. Confirmatory evidence was provided by the excretion of an excess of pressor admines in the urine, and tomography and air studies were used to localize the site of the tumour.

Finally, the difficult post-operative course emphasizes the importance of close collaboration between surgeon, anæsthetist and physician in the management of these cases.

REFERENCES

AIRD, I. (1957) A Companion in Surgical Studies. 2nd ed. Edinburgh and London; p. 1064.
HELPS, E. P. W., ROBINSON, K. C., and ROSS, E. J. (1955) *Lancet*, ii, 267.
SPRAGUE, R. G., KVALE, W. F., and PRIESTLEY, J. T. (1953) *J. Amer. med. Ass.*, **151**, 629.

**Postural Aphonia.**—A. G. GRANT, L.R.C.P.I., L.R.C.S.I. (for F. BOYES KORKIS, F.R.C.S.).

B. H., male, aged 22.

*Complaint.*—Hoarseness on rotating head to the left side.

*History.*—Motor-cycle accident June 17, 1956. Contusion of mouth and lips and broken right lateral and central incisors resulted. Not unconscious and no retrograde amnesia. Eight days later sudden onset of hoarseness. No cervical pain or swelling noted. Over the next six weeks hoarseness gradually decreased until it was only present on turning head to the left. Has persisted since then.

*On examination.*—Looking to the right he can speak with a firm clear voice, but if he is asked to turn his head slowly to the left while counting aloud there is increasing hoarseness which starts soon after crossing the mid-line and reaches complete aphonia when the head is fully rotated to the left. No external abnormality. No limitation of cervical spine. Indirect laryngoscopy shows a fixed fully abducted left vocal cord but both arytenoids move normally on respiration.

*Investigation.*—X-ray of cervical spine, skull and chest shows no abnormality. Laryngeal tomogram reveals widening of laryngeal sinus with flattening of left side of larynx. W. and Kahn negative. Neurological examination normal. Direct laryngoscopy: No falling forwards of the arytenoids which are both mobile on respiration. Left vocal cord flaccid, completely abducted and bowed. Elliptical gap increased when head turned to the left. Right vocal cord moved to mid-line on phonation.

*Conclusion.*—Partial nerve lesion due to compression of fibres of left recurrent laryngeal nerve from hæmatoma or œdema is a more likely cause than avulsion of muscles from the vocal process as the symptom did not occur until eighth day after accident. Compensation by the right cord is presumably incomplete when head is rotated to the left due to an increase in the gap.

*Proceedings of the Royal Society of Medicine* Vol. 51 183

# Section of Urology

President—LESLIE N. PYRAH, M.Sc., Ch.M., F.R.C.S.

[*October* 24, 1957]

## The Calcium-containing Renal Stone [*Abridged*]

### PRESIDENT'S ADDRESS

By LESLIE N. PYRAH, M.Sc., Ch.M., F.R.C.S.

*Leeds*

THE calcium-containing renal calculus, like chronic duodenal ulcer and many cases of hormone-controlled carcinoma of the prostate and of the breast, is not a local disease of a part of the organ concerned; such a stone is usually the result of pathological changes affecting the renal parenchyma as a whole, and sometimes it results from abnormalities in organs remote from the kidney, for instance the parathyroid gland.

For a long time the attention of the surgeon was mainly concerned with the local lesion, because of the pain that it caused and because it was so often associated with infection and ultimately with serious damage to the renal parenchyma. The practical difficulties which face the surgeon, as well as the need for wider knowledge, are shown by the following case:—

Fig. 1 shows the control film and also the intravenous pyelograms of a male patient aged 56 years, who had a stone in the upper left major calyx, upon whom it was intended, after considering the pre-operative radiograph, to do an upper polar partial nephrectomy, for the relief of pain, removing the stone together with the upper major calyx in which it lay. When the kidney was exposed at operation, in addition to a stone a small, yellow, cortical tumour of 3 cm. diameter, shown later to be either a small hypernephroma or a latent carcinoma of the kind described by Franks (1954), was discovered, so the kidney was removed. A radiograph of the kidney (Fig. 2) after removal demonstrates the complicated problem which faces the surgeon:

(1) The pre-operative radiograph suggested one stone, but in fact in at least three of the calyces (upper, middle and lower) there were multiple tiny stones or calcific foci.

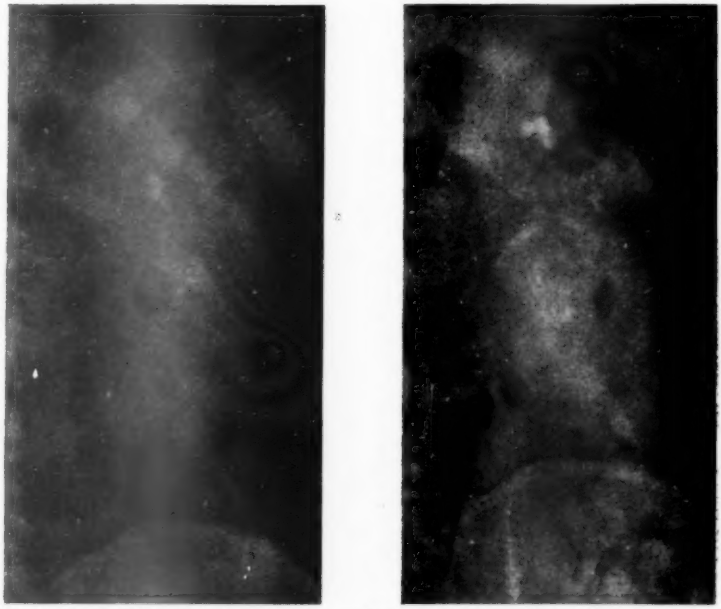


FIG. 1.—Straight X-ray and intravenous pyelogram of male patient, W. S. I., aged 56, showing a stone in the upper major calyx of the left kidney.





FIG. 2.—Radiograph of the excised kidney of the patient referred to in Fig. 1, showing in addition to the large stone in the upper calyx, multiple smaller calculi and calcific foci which had not been detected in the pre-operative radiograph.

(2) The partial nephrectomy operation which it was intended to do would not have dealt with these other gritty particles, nor have prevented their further maturation into large stones, nor indeed would any conservative operation.

(3) Although the largest stone was probably the cause of his pain, this was not certain. Nothing short of a nephrectomy would have removed all the calcific foci and thus have prevented further clinical symptoms later; yet the extent of the calcific process at the time of operation was not severe enough to indicate such a radical procedure in a well-preserved kidney had it not been for the presence of the tumour.

(4) The extensive, though mostly tiny, calcific deposits raise the question as to whether the patient may not develop stones in the remaining kidney at a later date. The second kidney is believed to be free from stones because of the control radiograph, but it may already harbour tiny calcific calyceal foci. Indeed, a guide to the prognosis in the remaining kidney is shown by his urinary calcium output after unilateral nephrectomy (Table I), which reveals a moderate hypercalciuria, unassociated with any elevation of his serum calcium; so it seems likely that the stone-forming potentiality still exists in his remaining kidney.

TABLE I.—BLOOD AND URINE CHEMISTRY IN A CASE WHOSE RADIOGRAPHS ARE SHOWN IN FIGS. 1 AND 2. There is a Moderate Hypercalciuria when the Patient is on a Normal Ward Diet. The Blood Calcium is Normal

W.S.I. ♂
Aged 59

| | BLOOD | | |
|---|---|---|---|
| Date | Calcium (mg%) | Inorganic phosphate (mg%) | Protein (g.%) |
| 20.9.56 | 9·9 | 2·2 | 6·6 |

| | URINE | | |
|---|---|---|---|
| Date | Calcium (mg/24 hr.) | Inorganic phosphate (mg/24 hr.) | Volume (ml.) |
| 15.9.56 | 321 | 1,111 | 2,020 |
| 16.9.56 | 431 | 1,450 | 2,230 |
| 17.9.56 | 374 | 1,550 | 2,215 |

The present surgical treatment of many and perhaps of most calcium-containing renal stones, however carefully the operation is done, is very often a relatively crude attack upon the disease designed primarily to relieve pain and to conserve renal function.

So it is proposed now, to examine some of the general factors (some of which may seem to be academic) concerning the stone-bearing kidney and also the calculus itself; then to refer to our limited knowledge of the general causes of stone; and finally to the attempts which are being made to prevent recurrent stone formation.

Most of the work here referred to has been done in the Department of Urology in Leeds by the clinical and research members of the Department, with important contributions from Dr. C. K. Anderson, Dr. A. Hodgkinson, Mr. B. T. Murphy and Mr. M. J. Purton.

## PATHOLOGY OF THE STONE-BEARING KIDNEY

The histological findings in the normal kidney are first compared with those found in the stone-bearing kidney at a time before it has been seriously damaged by disease. Nephrocalcinosis (by which is meant calcification in the renal parenchyma which is demonstrable

radiologically) and also renal calcification resulting from known extra-renal diseases, are excluded from consideration.

*The normal kidney.*—Does calcification occur in the *normal* kidney? The answer is that it does and very commonly. 380 apparently normal kidneys have been submitted to microscopic examination and tiny foci of calcification were present in a percentage which varied from 14% to 25% in different groups of autopsy cases according to the disease causing death; the overall incidence was about 15%. The calcific foci were sparsely scattered in the cells and sometimes around the upper collecting tubules, while a few lay within the lumina of the tubules; they are shown as black, globular deposits in almost normal cells (Fig. 3). The cause of these calcific deposits is unknown.

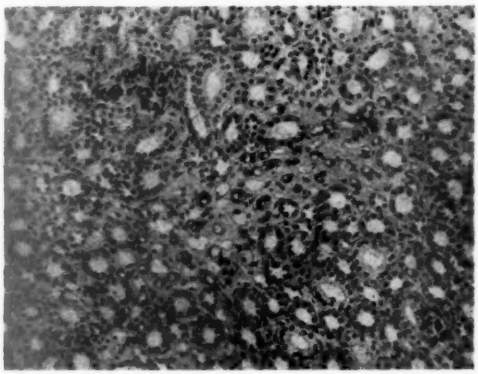
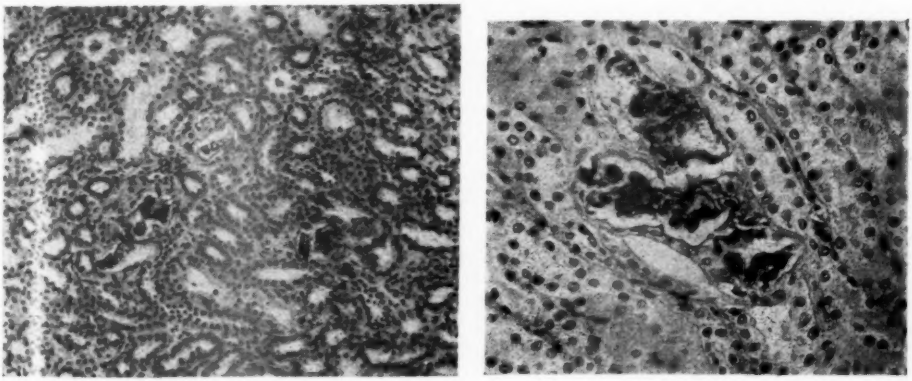


FIG. 3.—Microscopic section of a normal kidney showing two foci of calcification (stained black). ×80.

*The stone-bearing kidney.*—Examination of the renal parenchyma of partial nephrectomy specimens removed at operation for aseptic calcium-containing stones and also of stone-bearing kidneys removed at autopsy, has shown approximately a 75% incidence of calcification in the renal pyramids. The calcification here is usually found in the upper collecting tubules which may be dilated and contain calcium casts, occasionally in the convoluted tubules and also outside the tubular lumina, when they have ulcerated through (Fig. 4A and B). In the vast proportion of cases the calcific deposits in the stone cases are far more



A B

FIGS. 4A and B.—Microscopic section of a kidney which was the seat of a calyceal stone. There are multiple calcific foci in the renal papillæ (for description *see* text). A ×120. B ×200.

numerous and much closer together than the occasional sparse and scattered calcific deposits in normal non-stone-bearing kidneys. This intra-renal lesion is regarded as *the one* which is commonly associated with a calcium-containing stone.

In attempting to find the early lesion of the calyceal stone, Randall (1937) described plaques of calcium phosphate which started in the sub-epithelial region of the renal pyramids. Fig. 5 shows an example of such a plaque lying immediately beneath the



FIG. 5.—Photomicrograph of a renal papilla showing a Randall's plaque (stained black). ×93.



FIG. 6.—Thin section of a stone. The pale part at the hilus (right) of the stone is calcium phosphate derived from a Randall's plaque. The rest of the stone is laminated calcium oxalate.

calyceal epithelium and lifting it slightly as if preparatory to ulceration. Randall believed that the epithelium covering the plaque was subsequently lost and that upon the calcium phosphate nucleus thus exposed to the action of the urine, calcium oxalate or other urinary salts could be deposited, leading to the maturation of a calculus (Fig. 6). Of the many kidneys that have been examined, however, Randall's plaques have not been found with the frequency described by him.

A much rarer type of aseptic calcification of which only three or four examples have been found, is that seen in the kidney of a male patient aged 24, who had bilateral renal calculi. The urine was free from infection. Partial nephrectomy for the removal of the lower calyceal stone in the left kidney revealed, in addition to the large stone, three other calculi within a renal papilla, far removed from its calyceal epithelium (Fig. 7A). Microscopically there were a few intra-tubular calcific deposits but there was no cellular damage of the renal tubules except that caused by local trauma, and there was no inflammatory cellular response. Fig. 7B shows a deposit in a dilated duct of Bellini of some inspissated colloidal debris partly impregnated with calcium salts.



FIG. 7A.—Partial nephrectomy specimen showing two biggish and two smaller calculi located in the renal papilla itself and not in a calyx.

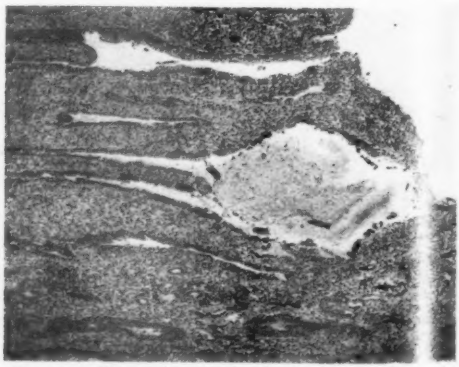


FIG. 7B.—Photomicrograph of the renal papilla the same case showing a dilated duct of Bellini containing colloidal debris partly impregnated with calcium salts (stained black). ×25.

These, then, are the three types of calcification which have been found in the aseptic stone-bearing kidney, and the first is considered to be the most important.

In the infected stone-bearing kidney, the picture is different; in such cases there is usually widespread calcification and microlith formation in the renal parenchyma, mainly in the pyramids. Fig. 8A shows the renal tract of a woman of 26 with calculous disease of both kidneys and one ureter; the clinical symptoms were not severe though she had a very resistant staphylococcal infection. The calcification here is distributed in the collecting tubules causing a complete blockage of the nephrons involved, and there are

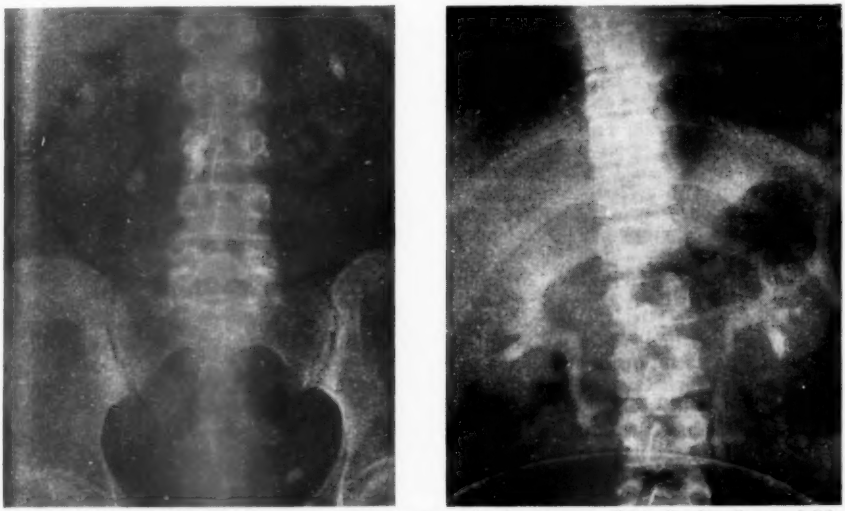


FIG. 8A.—Straight X-ray and intravenous pyelogram of urinary tract of M. G., female, aged 26. There was calculous disease of both kidneys and left pelvic ureter. The urine was infected.

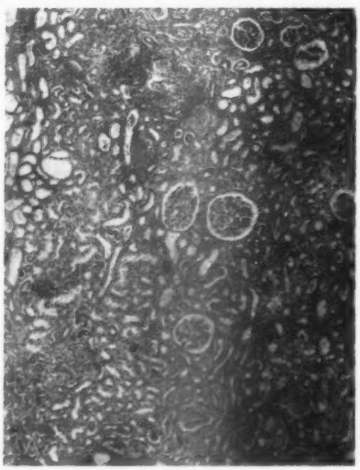


FIG. 8B.—Patchy foci of papillary calcification together with round cell infiltration in a kidney the seat of an infected stone (partial nephrectomy specimen obtained from the case in Fig. 8A). Low power.

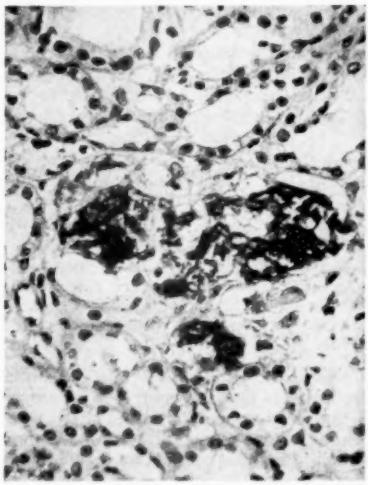


FIG. 8C.—As Fig. 8B. High power. ×233.

scattered foci in the convoluted tubules, usually the proximal ones (Fig. 8B and C). The infected cases show the grossest and most widely-spread calcification of any in the stone group; the deposits of calcific debris are larger and there is more general cellular reaction than in the non-infected stone group; there are foci of reactionary cells, often fibroblasts, without necessarily pus formation, and there is peritubular fibrosis.

Finally, calculi may be deposited in kidneys which are the seat of hydronephrosis or hydrocalycosis, possibly of congenital origin, and then stasis of particulate matter probably has an important role, intra-renal calcification not being any more common than in the normal kidney.

## Excretion of Urinary Calcium and Phosphorus in Stone Cases

Since it appears that in the parenchyma of the stone-bearing kidney there is a much greater tendency for calcium phosphate to be precipitated than in the normal kidney, the excretion in the urine of calcium and of phosphorus in patients with calcium-containing stones, and in normal controls, has been compared.

In addition to examining the urinary calcium and phosphorus in a series of cases on a low calcium diet, a larger series of urinary calcium and phosphorus on an ordinary ward diet has been examined, since the accommodation in the metabolic ward would not allow every patient with a renal calculus to be given the controlled diet. Certain conclusions have been reached regarding the practical value of the two methods, and criteria have been selected for a diagnosis of hypercalciuria on an ordinary ward diet.

*Normal urinary excretion of calcium.*—Fig. 9 shows the urinary excretion of calcium in a group of 132 normal men and 126 normal women on an intake of 800 ±200 mg. of calcium per day. The majority excreted between 100 and 200 mg. of calcium per day. On looking at the figures in greater detail, it was found that at least 90% of the men excreted less than 300 mg. per day, and at least 90% of the women excreted less than 250 mg. per day. A few individuals in each sex group excrete exceptionally large amounts of calcium, the incidence of these very high calcium values being greater in normal men than in normal women (Hodgkinson and Pyrah, 1958).

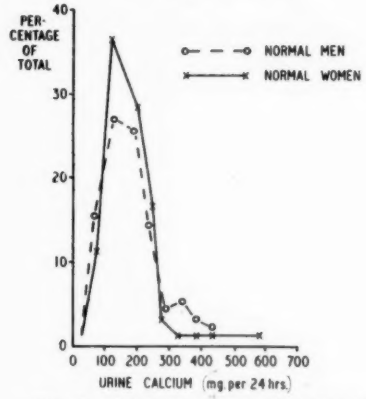



Fig. 9.—Urinary excretion of calcium in a group of 132 normal men and 126 normal women on an intake of 800±200 mg. of calcium per day (Hodgkinson and Pyrah, 1958).

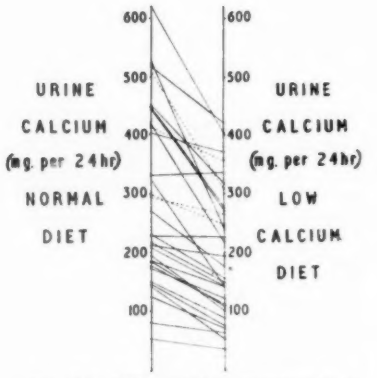



Fig. 10.—Urine calcium excretion in 32 patients on a ward diet and also on a low calcium diet (for explanation *see* text).

*Urinary excretion of calcium on normal and low calcium diets.*—The urinary calcium excretion was then compared in 32 stone patients firstly on a ward diet (containing 800±200 mg. calcium per day) and then on a low calcium diet (containing 130 to 170 mg. of calcium per day), and the results are shown in Fig. 10. The corresponding measurements for each individual on the two diets are joined by solid or dotted lines, the latter representing cases of stone in association with proved hyperparathyroidism. In general there is a decrease in the urinary calcium, but it is not necessarily a marked decrease; in some cases (in fact, in quite a proportion) there is little change.

It has already been shown that the approximate upper limit of normal for men is 300 mg. per day, and for women 250 mg. per day. If these values are accepted, then 14 of these 32 stone patients had abnormally high urine calcium values. Similarly on the low calcium

diet, it is considered that the approximate upper limit of normal is 175 mg. of calcium per day; so in the 32 patients considered here, 16 had urinary calcium values greater than 175 mg. The figures, therefore, for the incidence of hypercalciuria, when the estimations are done on a low calcium diet and also on a normal calcium diet, are reasonably close. It seems, therefore, that for practical purposes an abnormality of calcium excretion may be detected as readily with the patient on a normal diet as on a carefully controlled low-calcium diet.

*Calcium excretion by normal adults and by stone patients on a normal diet.*—Fig. 11A shows the distribution of urine calcium values for normal men compared with that of a group of 220 male stone patients. In the case of the stone patients there is a shift to the right, showing a higher incidence of hypercalciuria; 35% of the stone cases had values higher than 300 mg. compared with 10% of the normal controls.

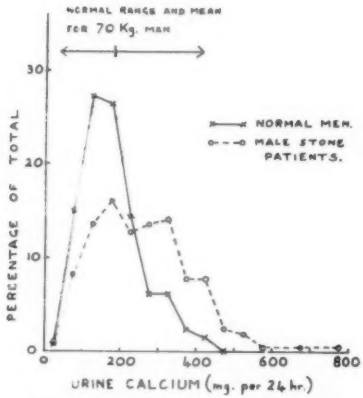



FIG. 11A.—Distribution of urine calcium values for normal men compared with a group of 220 male stone patients.

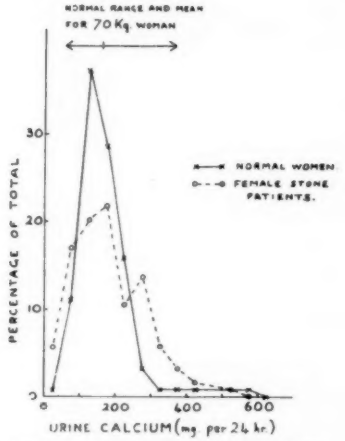



FIG. 11B.—Distribution of urine calcium values for normal women compared with a group of 124 female stone patients.

Fig. 11B shows the distribution of urine calcium values of normal women compared with those of 124 female stone patients. Once again there is a shift to the right in the stone patients showing an incidence of hypercalciuria, but this is not so marked as in the men. In fact 25% of the women with stone had values of urinary calcium higher than 250 mg. compared with 6% of normal women.

*Calcium excretion and impaired renal function.*—Stone patients with marked impairment of renal function had a low excretion of urinary calcium. When the urinary calcium is plotted against urea clearance, in no case was it found that the urine calcium was high when the urea clearance was low. Fig. 12 shows the relationship between urinary calcium

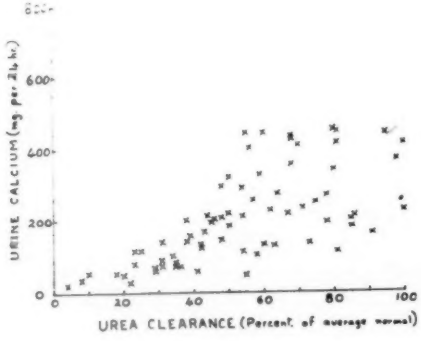



FIG. 12.—Relationship between urinary calcium excretion and urea clearance in 72 renal stone patients on a normal diet.

excretion and urea clearance for 72 patients on a normal diet. If the cases having poor renal function are omitted from the series, then it is found that the incidence of hypercalciuria is rather higher, namely 37% in the case of men stone-formers and 31% in the case of female stone-formers.

*Calcium excretion and type of stone.*—The incidence of urinary excretion of calcium and hypercalciuria was then compared with the type of renal stone (Table II). The incidence

TABLE II.—THE RELATIONSHIP BETWEEN THE URINARY EXCRETION OF CALCIUM AND THE TYPE OF STONE

| Group | Total No. of individuals | Percentage with urine calcium values greater than 200 mg. per day |
|---|---|---|
| Normal adults .. .. | 258 (56) | 26% (31%) |
| Calcium phosphate stones.. | 14 (11) | 30% (54%) |
| Calcium oxalate stones .. | 46 (26) | 53% (69%) |
| Mixed calcium oxalate and calcium phosphate stones | 53 (15) | 77% (93%) |
| Mixed struvite and calcium phosphate stones | 17 | 17% |

(Figures in brackets—Cottet and Vittu, 1955)

in the series is compared with that in a similar group of 52 calcium stone cases analysed by Cottet and Vittu (1955). It was found that the incidence of high urine calcium values was greatest in the mixed calcium oxalate—calcium phosphate calculi and almost as great in the pure calcium oxalate stones; hypercalciuria had the lowest incidence in cases composed of mixed magnesium ammonium phosphate and calcium phosphate; in the case of pure calcium phosphate calculi, the figures are intermediate, and in the last two groups most of the stones are the result of infection.

The findings agree with those of Cottet and Vittu (1955) but the incidence of high calcium values in each group in the series is lower than in the corresponding group reported in their series; and even when cases of impaired renal function in the series are omitted the figures of hypercalciuria are still lower than those of Cottet and Vittu.

Thus 66% of patients with calcium oxalate or mixed calcium oxalate—phosphate stones had average urine calcium values greater than 200 mg. per day compared with 26% of normal individuals. It is suggested, therefore, that in this group of cases of stone, hypercalciuria is an important contributory factor.

*Phosphorus excretion in normal individuals and in stone patients on a normal diet.*—The daily excretion of inorganic phosphate in healthy adults averages 800 mg. though there is a considerable variation above and below this value. The urinary excretion of inorganic phosphate is influenced by the dietary intake of phosphorus (though other factors also play a part) and it was estimated that an intake of phosphorus on the normal ward diet is within the range 1,100 ±300 mg. per twenty-four hours, which corresponds to a variation in the urinary excretion of inorganic phosphate of ±11%.

The distribution of the urinary phosphate per twenty-four hours, for 92 normal men and 118 normal women, on phosphorus intakes within the range of 1,100 ±400 mg. per day, is shown in Fig. 13 (Hodgkinson and Pyrah, 1958), the numbers of the cases being

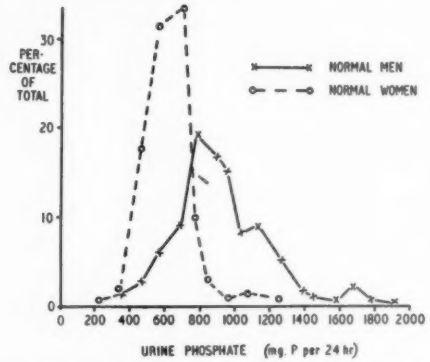



FIG. 13.—Urinary excretion of inorganic phosphate for 92 normal men and 118 normal women.

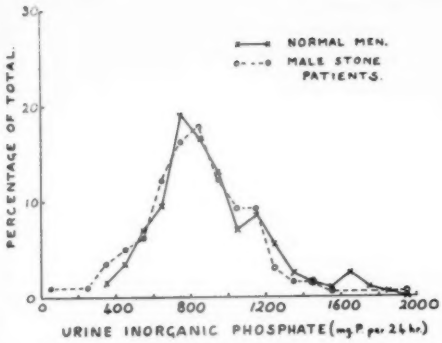



FIG. 14A.—Distribution of urinary phosphate for normal men compared with that for 198 renal stone male patients on normal ward diet.

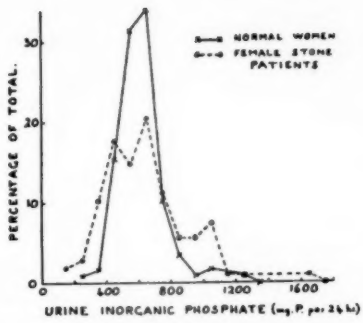



FIG. 14B.—Distribution of urinary phosphate for normal women compared with that for 108 female stone patients on a normal ward diet.

shown as a percentage of the total. The distribution of urine phosphate values for normal men varies between the figures of 450 and 1,600 mg. per twenty-four hours and thus differs significantly from that for normal women which varies between 350 and 950 mg. per twenty-four hours; so that in comparing the excretion in normal adults and in stone patients, allowances should be made for differences of sex.

Fig. 14A shows the distribution of urinary phosphate values for normal men compared with the distribution for 198 male patients with renal stones; the number of cases is again expressed as a percentage of the total. There is no significant difference in the phosphate excretion in the normal patients and in the stone patients.

Fig. 14B shows the distributions of urinary phosphate for normal women and for 108 female stone patients on a normal ward diet. A few of the female stone patients appear to have abnormally high values; thus 17 female stone patients (15·7%) had urine phosphate values greater than 900 mg. per day compared with 3·4% of the normal women. In 11 of these 17 patients the high phosphate excretion was associated with high calcium excretion and 4 of these had high or moderately high serum calcium values. One of them had, in fact, a parathyroid adenoma and the others are under continuous observation as possible cases of primary hyperparathyroidism.

The following points, therefore, have emerged from this investigation. The incidence of high urinary calcium excretion is appreciably greater in stone patients than in normal individuals and in men than in women. The incidence of hypercalciuria is greatest (60%) in cases of the aseptic calcium oxalate and the mixed calcium oxalate and phosphate stones. A high urinary excretion of calcium is not, however, found in *all* stone patients notably in those whose stones result from infection. A high urinary excretion of calcium is not *restricted* to patients with calcium stone since approximately 8% of normal adults were found to have urinary calcium values greater than 300 mg. for men and 250 mg. per day for women, whereas the incidence of calcium stones of renal origin in the general population is probably less than 0·2%. The evidence, however, suggests that the hypercalciuria is of ætiological importance for many renal calculi. Hyperphosphaturia does not appear to be a factor in the formation of calcium stones.

### Possible Causes of Hypercalciuria

If, then, hypercalciuria has an ætiological significance, we must search for the causes, but so far none has been found to explain the majority of cases. A few are the result of hyperparathyroidism, but such cases are usually diagnosed because of the raised serum calcium.

Some possible explanations of the hypercalciuria may be:

(1) That there is a high intake of calcium in the diet accompanied by a high absorption and a high urinary excretion of calcium. If, however, these hypercalciuric patients are placed on a low calcium diet, they still excrete a large amount of calcium. If increased absorption is due to sensitivity to vitamin D, it should be possible to reduce calcium absorption and therefore excretion by giving cortisone (Anderson *et al.*, 1954); in the cases, however, that have so far been submitted to this test, cortisone does not result in any reduction of calcium excretion, in fact, there may even be an increase.

(2) There may be a renal tubular defect in that calcium which is passed down the tubules in the glomerular filtrate is not reabsorbed in normal quantities by the tubular epithelium. Although Albright and Reifenstein (1948) postulated that in one group of cases of idiopathic hypercalciuria a mild infective pyelonephritis caused by the *Staphylococcus albus* had resulted in tubular damage, with resulting impairment of the calcium-reabsorption mechanism, we have not ourselves so far found much clear evidence of an infective origin of the hypercalciuria. If there is damage to the enzyme system responsible for the reabsorption of calcium by the tubules, it is possible that other tubular functions are also damaged, and we have some evidence to support this view, and it is under active investigation.

(3) The third working hypothesis is that there is some abnormal form of calcium in the blood which is excreted from the blood stream by way of the glomerular filtrate and with which the renal tubules cannot deal; the calcium, therefore, passes into the urine in abnormally high amounts. Thus, if calcium is bound to citrate or to another organic acid in excessive amounts, the tubules may not be able to reabsorb it. In such cases the urine might be expected to contain an excess of the organic radical to which the calcium is bound. This possibility is under investigation.

It is impossible here to go into greater detail either in regard to the fundamental cause of the hypercalciuria, or even in assessment of the clinical diagnosis of such cases; the following case illustrates the difficulties with our present available resources:

*Case report.—A. W.*, a man aged 48, had a nephrolithotomy for the removal of an oxalate calculus in 1953; recurrent stones were found in 1954 and these are still present. He was then found to have marked hypercalciuria.

The blood chemistry has been investigated thirty-two times since 1953, the only abnormalities found being a moderately elevated alkaline phosphatase (10 to 18 King-Armstrong units), and a slightly raised serum calcium (10·5 to 11·0 mg. %). We considered the possibility that the moderately elevated serum calcium level and the excessive urinary excretion of calcium (600 to 800 mg. per day) might be due to *multiple myeloma* but there were no bone changes, no Bence-Jones protein in the urine and no abnormality in the serum proteins.

A moderate glycosuria was found, but Cushing's disease was excluded on clinical grounds and also because the glucose tolerance curve was found to be normal and it seemed probable that the glycosuria was renal in origin.

Calcium, phosphorus, and nitrogen balance studies were carried out in 1955 (Fig. 15A). On a low calcium diet the patient was in marked negative calcium balance, the urine calcium averaging

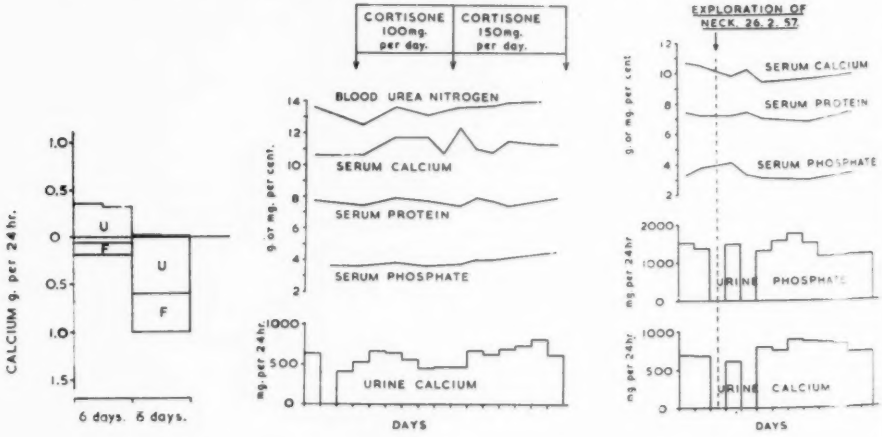



FIG. 15 (Case A. W.).—A, Calcium balance study on low and normal calcium intake. F=faeces. U=urine. B, effect of cortisone on serum calcium and urine calcium showing biochemical changes in the urine (for full explanation *see* text). C, Blood chemistry.

400 mg. per day compared with normal values of 100 to 150 mg. per day. On a normal calcium intake (1,000 mg. per day) however, the patient was in balance. The ratio of urinary to faecal calcium was greater than normal which suggests that the patient is able to maintain himself in balance on a normal calcium intake by absorbing a greater proportion of the dietary calcium than is usual, hence the absence of bone decalcification.

Is it possible that an excessive absorption of calcium from the gut is the primary defect? Anderson *et al.* (1954) and Henneman *et al.* (1956) have shown that in sarcoidosis, which

occasionally leads to renal stone formation, hypercalcæmia and hypercalciuria are due to excessive intestinal absorption of calcium, the condition resembling hypervitaminosis D. In such cases treatment with cortisone, 100 to 150 mg. per day for one to two weeks reverses this excessive absorption and results in a decrease in the intestinal absorption of calcium and a reduction in the serum and urine calcium levels. In the present case, treatment with cortisone, 100 mg. per day for six days followed by 150 mg. for a further seven days, resulted in a slight rise in both the serum and urine calcium levels (Fig. 15B). It was concluded from this investigation that excessive intestinal absorption of calcium from any cause is not the primary defect in this case; sarcoidosis as a diagnosis also appeared to be excluded.

An increase in the serum calcium level may occur when cortisone is given to patients with primary hyperparathyroidism and the possibility of parathyroid adenoma was considered. The serum calcium level of this patient varied within the range of 10·5 to 11·0 mg.% (Fig. 15C). Until recently we had considered this to be a high normal value but Keating (1955) in reporting the Mayo Clinic findings, has described many cases of primary hyperparathyroidism with average serum calcium values within this range; it was therefore decided to explore the neck for a possible parathyroid adenoma, which was done in February of this year. No evidence of parathyroid adenoma or hypertrophy was found. Following the operation the serum calcium level fell to 9·5 mg.%, but the urine calcium remained high at about 800 mg. daily. It was concluded that this is probably *not* a case of primary hyperparathyroidism although one must bear in mind the considerable difficulty which the surgeon has in locating the very smallest parathyroid adenoma.

On the evidence so far obtained this case would appear to be a true case of idiopathic hypercalciuria.

## Crystallography

Turning now to the stone itself, crystallographic methods of study have enabled its mineralogical nature and its structure and mode of growth to be studied in about 400 cases of renal calculi. The techniques used have been those of X-ray diffraction, the polarizing microscope, studies of thin sections, and microradiography. The composition of calculi using similar methods has been previously investigated by Jensen (1938, 1940, 1941), Prien and Frondel (1947) and Prien (1949), Carlstrom (1955) and Lagergren (1956).

(1) *X-ray analysis.*—By irradiating finely powdered, crystalline material prepared from different parts of the stone, with a beam of monochromatic X-rays, the rays diffracted from the intra-atomic planes of the crystal lattice can be recorded upon a photographic film as a series of lines of variable spacing and intensity, producing a powder pattern which is distinctive for each crystalline substance. This method has enabled it to be shown that there are two different types of oxalate. Chemically the two oxalates are calcium oxalate monohydrate (whewellite) and calcium oxalate dihydrate (weddellite).

Calcium phosphate occurs in three forms which can be distinguished by this technique, namely calcium hydrogen phosphate dihydrate, tricalcium phosphate and apatite (a complex phosphate probably with adsorbed carbonate). The common triple phosphate is magnesium ammonium phosphate hexahydrate or struvite.

(2) *Polarizing microscope.*—A few particles of finely powdered samples of different parts of the calculi (the nucleus or the various layers) are immersed in a liquid of known refractive index under a cover slip, and a comparison is made between the two refractive indices for the purpose of identification. This is the most sensitive method for the study of small amounts of crystalline material.

(3) *Thin-section techniques.*—A thin-section technique has been used for the study of 96 cases of stone. The stone is first embedded in Perspex (methyl methacrylate); various other resins have also been tried; part of the stone is cut away and the flat cut surface is secured to a glass slide. The opposite pole of the stone is then cut or filed away until a section the thickness of 10$\mu$ is obtained which is then examined through the polarizing microscope.

(4) *Micro-radiography.*—Using the techniques of micro-radiography of thin sections of stones, 25 cases have so far been examined and this study is continuing. Different components of the stones will absorb the rays in different proportions and these differences are recorded on the film.

*Calcium oxalate calculi.*—Their crystallographic structure has been found to be of two types, in which the habits of the crystals differ, suggesting that the calculi are formed by two different mechanisms. In Type I, the stone, which is composed of calcium oxalate monohydrate (whewellite) only, has a nodular surface; the fractured surface often shows that the stone has a laminated structure, the laminæ being upwards of 1 $\mu$ thick; radial striation is characteristic. This type of stone is believed to have been formed by crystals deposited in a colloid matrix, the slow diffusion of ions taking place to form the needle-like crystals which grow out from the centre (Fig. 16).

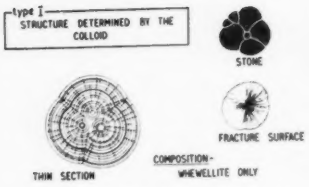



FIG. 16.

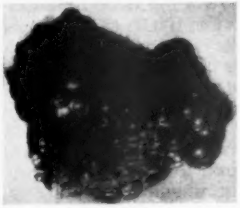


FIG. 17A.

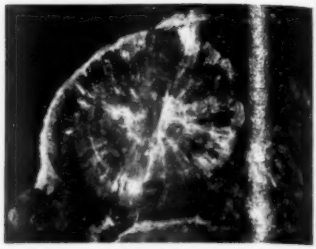


FIG. 17B.

FIG. 16.—Calcium oxalate stone (Type I). The structure is determined by colloid. The stone has a nodular surface and cross section shows lamination and radial striation.

FIG. 17A.—Calcium oxalate stone (Type I), magnified, showing nodular surface.

FIG. 17B.—Fractured surface showing radial striation and lamination.



FIG. 18.

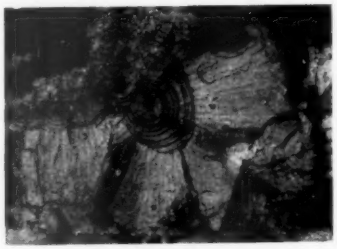


FIG. 19.

FIG. 18.—Thin section of nodular calcium oxalate stone (Type I). There is well-marked lamination and radial striation. ×15.

FIG. 19.—Calcium oxalate monohydrate stone (Type I). There is radial striation from the centre to the periphery. The lamination is limited to the central part of the stone. ×15.

Fig. 17A shows a stone having the characteristic nodular surface of a Type I oxalate stone. Fig. 17B shows the fractured surface revealing both the lamination and the radial striation. Fig. 18 is a thin section of a Type I stone; the centre is a mass of crystals of calcium monohydrate which were originally dihydrate; the characteristic radial striation and the lamination is shown. The dark lines between the laminæ represent the colloid matrix.

Fig. 19 (Type I stone) shows a laminated nucleus of calcium oxalate monohydrate (whewellite), of which the entire stone is composed. There is radial striation which is characteristic of the type of stone from the centre to the extreme periphery, so there is no interruption in the fundamental structure of the calculus; the striation is due to long acicular crystals growing close together, disposed radially. The colloid in the centre is concentrated in the dark rings. The lamination here is unusual, since it usually extends throughout the entire stone.

In Type II oxalate calculi the crystallographic appearances are different from those in Type I. Here, there is either a disorganized mass of calcium oxalate dihydrate (weddellite) crystals alone; or the interstices between the dihydrate crystals are filled with colloid, or with calcium phosphate (apatite) and colloid; or such a stone serves as a nucleus for a further deposition of a laminated zone, the layers alternating between apatite (calcium phosphate) and calcium oxalate dihydrate. The appearances of these stones with their perfectly normal crystals and no embedding colloidal mass, suggest that the dihydrate has been formed by a primary crystallization process and not by secondary crystallization in a gel or by passing through an intermediate colloidal phase. The stone itself has a coarse or a fine crystalline surface, with the crystals also visible on the fractured surface; radial striation is absent and the fine lamination of the monohydrate stone is also absent; sometimes there is rough layering (Fig. 20).

Fig. 21A shows the typical crystalline surface of a Type II stone. Fig. 21B shows the fractured surface; the white patches are layers of apatite which appear powdery; the rest of the stone is composed of colourless or yellowish crystals of dihydrate (weddellite); the rather crude layering indicates stages of growth in the stone.

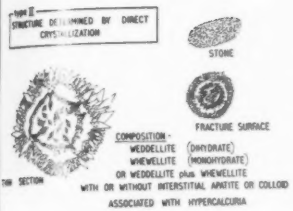



FIG. 20.



FIG. 21A.

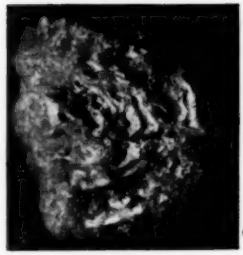


FIG. 21B.

FIG. 20.—Calcium oxalate stone (Type II). The structure is determined by crystallization. The surface is highly crystalline. The fractured surface is also crystalline. There is rough layering rather than well-marked laminations and there is no radial striation.

FIG. 21A.—Calcium oxalate stone (Type II). The surface is highly crystalline.

FIG. 21B.—The fractured surface shows crude layering. The white patches are apatite (calcium phosphate).

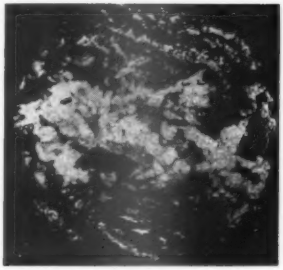


FIG. 22A.

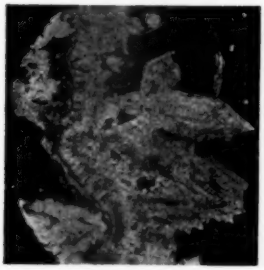


FIG. 22B.

FIG. 22A.—Thin section of calcium oxalate stone (Type II). (For description *see* text.)

FIG. 22B.—Thin section of calcium oxalate stone (Type II) showing much crystallization by calcium oxalate dihydrate. On the surface of the stone (right of the picture) lines parallel to the edge represent growth lines in the crystallization.

Fig. 22A shows an example of a Type II stone, namely a mixed calcium oxalate dihydrate and apatite stone (weddellite type). The crystals in the right centre of the field were large calcium oxalate dihydrate (weddellite) crystals, which have undergone recrystallization into the much smaller crystals of calcium oxalate monohydrate (whewellite). It is possible that the whole of the centre area in the field has been one large crystal of the dihydrate (weddellite) which has subsequently undergone recrystallization into monohydrate. The black parts in the field are again either colloid or apatite or a mixture of both. The small crystals in the upper and lower part of the field are of the monohydrate (whewellite).

The single crystals of the dihydrate (weddellite) are often especially obvious at the surface of these Type II calcium-oxalate-containing stones. The large crystals show lines which indicate their growth. The black part is either colloid or apatite (calcium phosphate) or a mixture of both (Fig. 22B).

If it is true that the Type II stones have been formed by primary crystallization, one would expect them to be associated with a high concentration in the urine of the stone-forming material. It has been found, in fact, that stones of this group are associated with hypercalciuria.

It is thought, therefore, that there are two types of calcium oxalate stone which are recognizable because of their structure by crystallographic techniques and which are probably aetiologically distinct. In the Type I stones it is suggested that the structure of the stone has been determined by the colloid; and that the incidence of hypercalciuria is no greater than in normal people. In this group, investigations into the urinary colloids may repay further study. In the Type II cases in which the structure of the stone appears to have been determined by direct crystallization, it has been found that the incidence of hypercalciuria is high, suggesting, in fact, that it is of aetiological importance.



FIG. 23.—Calcium phosphate stone showing fractured surface of calcium phosphate and magnesium ammonium phosphate hexahydrate. ×2.



FIG. 24.—Thin section of a struvite stone (magnesium ammonium phosphate hexahydrate). (For description *see* text.) ×3·5.

*Calcium phosphate calculi.*—Fig. 23 is a stone (cut across) composed of calcium phosphate (apatite) and magnesium ammonium phosphate hexahydrate (struvite).

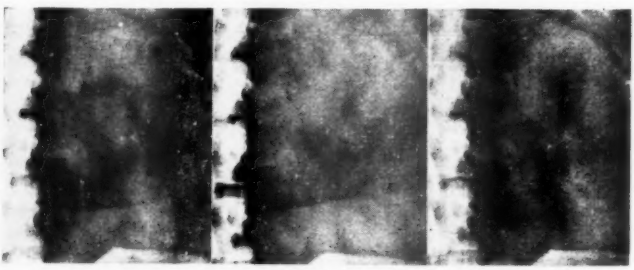
The structure of a phosphate stone is shown by the thin section of a struvite stone (Fig. 24). When the thin section is examined under polarized light, the stone has a laminated structure, with comparatively large single crystals of magnesium ammonium phosphate hexahydrate (struvite) arranged in rows along each band, the crystals being embedded in colloid or in apatite. The appearances suggest that each layer was deposited in the manner described by Schade, namely the primary formation of a nucleus followed by the deposition of successive layers of colloid, with crystal deposits in each layer.

## PREVENTION OF STONE FORMATION

The principles that have been used for the prevention of stone have been firstly to try to provide physical conditions in the urine either by methods of dilution or by alterations of the pH, which will make it unlikely that the stone-forming substances will be precipitated. An alternative method is to deny access to the urine of stone-forming substances such as phosphorus and calcium.

It is, however, interesting to refer to what actually happens in badly functioning kidneys if a stone-forming substance such as calcium is denied normal access to the urine because of poor renal function, and alternatively what happens if a good deal of calcium is presented to such a kidney simply because it happens to be in the blood stream.

Fig. 25 shows two small calcium-containing calculi inadvertently left behind at operation



23.6.48. 8.1.53. 9.9.54.

FIG. 25.—Two small calculous particles left behind at operation in a very badly functioning kidney. The stone disappeared without further interference (*see* text).

in a patient who had only one badly functioning kidney which was also infected with *Bacillus proteus*; in spite of the infection the stones were no longer visible radiologically when the patient was X-rayed three years later; they had probably undergone dissolution. The urinary excretion of calcium here was very small.

Similarly renal calculi never occur in kidneys which are the seat of chronic nephritis (unless, of course, the calculus has ante-dated the nephritis), because of the inability of the diseased kidneys to allow calcium to pass into the urine in any quantity. On the other hand, if in a patient who has advanced glomerulonephritis, large amounts of calcium are absorbed from the gut into the blood stream following, say, a very high intake of milk

calcium salts may be deposited in the glomeruli producing a stippled type of calcification throughout the entire parenchyma of the kidneys (Fig. 26); and also in such cases the excess



FIG. 26.—Bilateral calcification in both kidneys in a case of glomerulonephritis. The patient had had a high intake of calcium by mouth for a prolonged period. (By kind permission of Dr. Sosman, Peter Bent Brigham Hospital, Boston, U.S.A.)

of calcium salts may be deposited in subcutaneous and peri-articular tissues in an attempt to prevent the elevation of the serum calcium.

This summary will refer, briefly, to the ancillary methods which are being tried out to prevent the recurrence of calcium-containing renal calculi.

(1) *High intake of fluids.*—It is always advised that the stone-former should have an appreciably higher daily intake of fluids than a normal individual; apart from cystine stones (Dent, 1955), however, it is doubtful if sufficient urine volume can be achieved to obtain dissolution of existing calculi, though fluid may prevent the growth of crystalline matter into stones. An extreme example of the effect of a very high intake of fluids in the rat was shown by a simple experiment by Grove *et al.* (1950); these workers were able to induce bladder stones in rats by implanting tiny pieces of zinc through a suprapubic cystotomy; by substituting a solution of glucose for tap water for drinking which, by inducing thirst, caused a very high total daily intake of fluid, stones were prevented from forming around the zinc implants, and one-third of pre-formed calculi underwent dissolution.

(2) *Diet control: acidogenic diet.*—Higgins (1943) advocated an acid-ash diet to try to reduce the recurrence rate of renal calculi following operation. If the urinary pH is reduced, however, the increase in the urinary calcium which results may neutralize or outweigh any favourable effect from the change in pH. Moreover the urinary calcium salts do not differ in their solubility with the available range of pH to the same extent as do cystine and uric acid, so that the change in pH cannot be expected to give remarkable results.

In the case of some soft, non-infected, recumbency calculi consisting of almost pure calcium phosphate and a minimum of colloid (which are uncommon), the administration of ammonium chloride in biggish doses to render the urine acid, with or without an acidogenic diet, may effect a complete disintegration or dissolution of the calculi. A similar dissolution of soft phosphatic renal stones in certain cases of hyperparathyroidism with advanced skeletal changes, has been obtained; and such a treatment is the most reliable method of dealing with severe cases of phosphatic incrustation of the bladder.

(3) *Calcium excretion.*—Henneman *et al.* (1956) proposed the use of phytic acid (inositol phosphoric acid) for reducing urinary calcium excretion in sarcoidosis, in which the hypercalciuria is probably due to the excessive absorption of calcium from the intestine (Anderson *et al.*, 1954), and they suggested that this compound might be of value in the treatment of idiopathic hypercalciuria. In idiopathic hypercalciuria, however, it would appear that the defect differs from that in renal sarcoidosis in that it is renal rather than intestinal, so that the use of phytic acid in that condition would be of limited value.

(4) *Phosphate excretion.*—It has already been shown that in normal individuals and in stone patients the urinary excretion of phosphate is usually within normal limits. It is possible, however, that a reduction of the urinary phosphate may be of value in the treatment of recurrent calcium phosphate stone and the use of aluminium hydroxide gels is being recommended in suitable cases. This treatment can be used so as to cause an appreciable reduction in urinary phosphate by precipitating phosphate in the gut, but we find that it is sometimes accompanied by an increase in urinary calcium which is undesirable.

Various preparations of aluminium hydroxide are available (Pyrah and Smith, 1956) and the use of Hyalgel, which has the highest content of aluminium hydroxide with adsorbed carbonate has been preferred. This preparation is best used for the treatment of calcium-phosphate stones and probably it is not indicated with oxalate calculi. There has been

difficulty in inducing patients to stay on this treatment for long periods of time. Moreover it has not been certain that the treatment is of permanent value when there is a persisting urinary infection which cannot be cured. There has been a tendency, therefore, to limit the use of this treatment to co-operative patients in whom the urinary tract is free from infection and who also can attend hospital for adequate supervision.

Fair success has been achieved in reducing the phosphaturia. It is essential that the Hyalgel be given with meals in order to produce the maximum reduction of the urinary phosphate. It is also necessary for frequent tests on twenty-four-hour specimens of urine for phosphorus to be made. Fig. 27 shows the measure of reduction in urinary phosphate

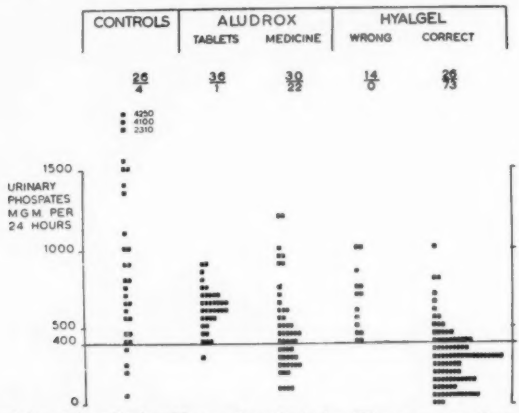



FIG. 27.—Effect of aluminium hydroxide on phosphaturia. The amounts of phosphate in the urine (mg./twenty-four hours) of 25 patients with renal stone while taking a normal diet with various preparations of aluminium hydroxide. 232 tests are each represented by one small square. Column 1, no aluminium therapy; column 2, Aludrox tablets; column 3, Aludrox medicine; column 4, Hyalgel taken inadequately or not with meals; column 5, Hyalgel 30 ml. q.i.d. with meals. 400 mg./twenty-four hours considered satisfactory, fractions represent the proportions of unsatisfactory to satisfactory results.

which can be achieved, and it has been found that Hyalgel is much better in this regard than Aludrox in doses which patients will tolerate.

Of 9 patients treated for periods of one and a half to three and a half years under what are regarded as optimum conditions, the clinical histories are as follows: These 9 patients between them have had 24 operations for stone; they had voided between them at least nineteen other stones. 3 patients had had nephrectomy and 4 had had partial nephrectomy. During the period of treatment one stone diminished markedly in size. Only one new stone has appeared in the 9 patients and this occurred during a period when treatment was not controlled; no existing stone has increased in size. The treatment, therefore, in a small group of patients, with the provisos that have been mentioned, is worth while, provided the criteria mentioned are also observed.

(5) *Oxalic acid excretion.*—Because of the lack of a suitable method for estimating oxalic acid in urine, few studies have been made of oxalic acid excretion in stone patients. A method has been recently developed which is considered to be sufficiently sensitive and specific. It has been found that urinary oxalic acid excretion is generally within normal limits in stone patients but that it may be slightly raised in patients with pure calcium oxalate stone. It is possible, therefore, that a reduction in the urinary excretion of oxalic acid may be of benefit in such cases; we have not yet tried this approach. Archer *et al.* (1957) described a case of hyperoxaluria in which there were 200 mg./day oxalic acid excreted in the urine (the normal figures being about 20 mg./day) and they reported that oxalic acid excretion could be reduced by feeding benzoic acid; the condition appears to be rare.

(6) *Excretion of organic acids:* (*a*) *Glucuronic acid.*—It is well recognized that, for reasons which are only partly understood, biological fluids including urine have a greater ability than water to hold calcium salts in solution. Mandl *et al.* (1953) emphasized the importance of organic acids in this process and Prien and Walker (1955) suggested that the ability of urine to hold calcium salts in solution might be enhanced by increasing the urinary excretion of glucuronic acid by the ingestion of salicylic acid. Trials in cases of recurrent stone have, however, shown that there is no significant reduction in recurrence rate when the excretion of glucuronic acid is thus increased (Vermeulen *et al.*, 1957).

(*b*) *Citric acid.*—Citric acid, which is excreted in the urine in amounts varying from 400 to 1,000 mg. per day, is one of the organic acids which probably plays an important part in helping to maintain calcium salts in solution. The excretion of citric acid is reduced in many cases of renal stone, and Shorr (1945) proposed the use of œstrogens to increase the urinary excretion of this acid. Conway *et al.* (1949) thought that the reduced excretion of citric acid could be explained by the presence of a urinary infection in these cases, but probably the infection does not account for all the low values which are found and further studies are being carried out on this aspect of the problem.

(7) *Calgon.*—The possibility of using the water-softener Calgon (sodium hexametaphosphate) as a therapeutic agent in the treatment of stone has been studied in our department (Care and Wilson, 1956). Calgon has the property of forming a soluble complex with calcium by an ion exchange process, and it was found that the experimental formation of stones in rats could be prevented by the addition of small quantities of Calgon to the drinking water. The suppression of stone formation was, however, accompanied by slight calcification in the renal parenchyma which was clearly undesirable. It may be possible to prevent this by using lower concentrations of Calgon and further long-term trials are proposed.

(8) *Chelating agents.*—Chelating agents are able to form complexes with various metals including calcium, and it is thought that this process may play a part in the formation or prevention of stones. Whereas in the case of phytic acid, citric acid, and Calgon, the combination with calcium involves an exchange of ions or the formation of a salt, chelation involves the formation of a ring structure with co-ordination linkages. The compound ethylene diamine tetra-acetic acid (E.D.T.A.) is a typical chelating agent commonly used for the decalcification of tissues *in vitro*. McGeown and Bull (1957) suggested that some of the urinary amino-acids may hold calcium in solution by forming soluble chelates, and reported that the urinary excretion of amino-acids is reduced in some stone patients. It is possible, therefore, that beneficial results might be obtained in some cases by increasing the urinary excretion of amino-acids if that is found to be possible.

ACKNOWLEDGMENTS.—The author desires to acknowledge the help and co-operation received from Dr. C. K. Anderson, Dr. A. Hodgkinson, Mr. B. T. Murphy and Mr. M. J. Purton.

## REFERENCES


ALBRIGHT, F., and REIFENSTEIN, E. C. (1948) Parathyroid Glands and Metabolic Bone Disease. Baltimore.

ANDERSON, J., HARPER, C., DENT, C. E., and PHILPOT, G. R. (1954) *Lancet*, ii, 720.

ANDERSON, L., and MACDONALD, J. R. (1946) *Surg. Gynec. Obstet.*, **82**, 275.

ARCHER, H. E., DORMER, A. E., SCOWEN, E. F., and WATTS, R. W. E. (1957) *Lancet*, ii, 320.

BAKER, R., and SISON, F. (1954) *J. Urol.*, **72**, 1032.

CARE, A. D., and WILSON, G. (1956) *Clin. Sci.*, **15**, 183.

CARLSTROM, D. (1955) *Acta radiol., Stockh.*, Suppl. 121.

CONWAY, N. S., MAITLAND, A. I. L., and RENNIE, J. B. (1949) *Brit. J. Urol.*, **21**, 30.

COTTET, J., and VITTU, C. (1955) *Pr. méd.*, **63** (i), 878.

DENT, C. E. (1955) *Brit. J. Urol.*, **27**, 317.

FLOCKS, R. H. (1939) *J. Amer. med. Ass.*, **113**, 1466.

FRANKS, L. M. (1954) *Ann. R. Coll. Surg., Engl.*, **15**, 236.

GROVE, W. J., VERMEULEN, C. W., GOETZ, R., and RAGINS, H. D. (1950) *J. Urol.*, **64**, 549.

HENNEMAN, P. H., DEMPSEY, E. F., CARROLL, E. L., and ALBRIGHT, F. (1956) *J. clin. Invest.*, **35**, 1229.

HIGGINS, C. C. (1943) Renal Lithiasis. Springfield, Ill.

HODGKINSON, A., and PYRAH, L. N. (1958) *Brit. J. Surg.* In the press.

JENSEN, A. T. (1938) *Z. Urol.*, **32**, 659.

—— (1940) *Acta chir. scand.*, **84**, 217.

—— (1941) *Acta chir. scand.*, **85**, 473.

KEATING, F. R. (1955) In: Post-Grad. Seminar, North Central Section of Amer. Urol. Ass. Minneapolis. p. 126.

LAGERGREN, C. (1956) *Acta radiol., Stockh.*, Suppl. 133.

MCGEOWN, M. G., and BULL, G. M. (1957) *Brit. med. Bull.*, **13**, 53.

MANDL, I., GRAUER, A., and NEUBERG, C. (1953) *Biochem. biophys. Acta*, **10**, 540.

NICHOLAYSON, R., EEG-LARSEN, N., and MALM, O. J. (1953) *Physiol. Rev.*, **33**, 424.

PRIEN, E. L. (1949) *J. Urol.*, **61**, 821.

——, and FRONDEL, C. (1947) *J. Urol.*, **57**, 949.

——, and WALKER, B. S. (1955) *J. Urol.*, **74**, 440.

PYRAH, L. N., and SMITH, I. B. (1956) *Brit. J. Urol.*, **28**, 231.

RANDALL, A. (1937) *Surg. Gynec. Obstet.*, **64**, 201.

RUBIN, P. S., and HOWARD, J. E. (1950) *Trans. Josiah Macy Conf. Metabolic Interrelations*, **2**, 155.

SHORR, E. (1945) *J. Urol.*, **53**, 507.

SOSMAN, M. E. (1947) *Amer. J. Roentgenol.*, **58**, 33.

SUTHERLAND, J. W. (1954) *Brit. J. Urol.*, **26**, 22.

VERMEULEN, C. W., FINLAYSON, B., and CHAPMAN, W. (1957) *J. Urol.*, **77**, 685.

VERMOOTEN, V. (1942) *J. Urol.*, **48**, 27.

[*November* 28, 1957]

THE following Specimens were shown:

(1) **Tuberculous Kidney Associated with Tuberculous Peritonitis.** (2) **Congenital Bladder-neck Obstruction, Urethral Diverticulum, Renal Osteodystrophy.**—Mr. L. N. PYRAH.

(1) **Ruptured Renal Cyst.** (2) **Hæmorrhage into a Renal Cortical Adenoma.**—Mr. HOWARD G. HANLEY and Dr. R. C. B. PUGH.

**Two Cases Illustrating the Value of Nephrotomograms.**—Mr. W. F. W. SOUTHWOOD.

(1) **Papillary Carcinoma of Renal Pelvis and Ureter.** (2) **Calcified Hæmatocele.** (3) **Papilloma of the Ureter Associated with Papilloma of the Bladder.**—Mr. BASIL PAGE.

**Three Cases of Anterior Urethral Valves.**—Mr. D. INNES WILLIAMS.

(1) **Carcinoma of Ureter.** (2) **Kidney and Ureter Eleven Years After Ureter had been Divided, Ligatured and Replaced During an Abdominal Operation.**—Mr. J. H. CARVER.

## BOOKS RECEIVED FOR REVIEW

**Boyd (B. F.)**, ed. Highlights of ophthalmology. Vol II, No. 1. pp. 116. Panama. Annual subscription $5.00.

**Council for International Organizations of Medical Sciences.** Connective Tissue. (Edited under the direction of R. E. Tunbridge.) pp. xii+371. Oxford: Blackwell. 42s. 0d. 1957.

**Council for International Organizations of Medical Sciences.** The planning of international meetings. pp. 114. Oxford: Blackwell. 7s. 6d. 1957.

**Dempster (W. J.).** An introduction to experimental surgical studies. pp. 463. Oxford: Blackwell. 50s. 0d. 1957.

**Dental Practitioners' Formulary 1957.** For use in the National Health Service. pp. 50. London: Pharmaceutical Press. 3s. 0d. 1957.

**Dunlop (D. M.), et al.**, eds. Textbook of medical treatment. 7th edit. pp. xix+924. Edinburgh and London: Livingstone. 55s. 0d. 1958.

**Hudson (E. H.).** Non-venereal syphilis. A sociological and medical study of bejel. pp. viii+204. Edinburgh and London: Livingstone. 30s. 0d. 1957.

**Hunt (A. H.).** Portal hypertension. pp. xi+230. Edinburgh and London: Livingstone. 40s. 0d. 1957.

**Huxley (J.).** Biological aspects of cancer. pp. 156. London: Allen & Unwin. 16s. 0d. 1958.

**Kinsell (L. W.)**, ed. Hormonal regulation of energy metabolism. pp. xiii+242. Springfield: Thomas. Oxford: Blackwell. 40s. 0d. 1957.

**L'Eltore (G.), *et al.*** Statistica e sociologia sanitaria. 2nd edit. pp. xvi+443. Rome: Centro Studi di Statistica Sanitaria de la Federazione Italiana contro la Tuberculosi e del Centro Studi di Sociologia Sanitaria. L. 3,000. 1956.

**Milton (R. F.).** Trace elements in soil, plant and animal. The Sanderson-Wells Lecture delivered at the Middlesex Hospital Medical School. pp. 14. London. 1957.

**Nabarro (J. D. N.).** Biochemical investigations in diagnosis and treatment. pp. xi+299. 2nd edit. London: Lewis. 25s. 0d. 1958.

**Oswald (N. C.)**, ed. Recent trends in chronic bronchitis. pp. vii+200. London: Lloyd-Luke. 30s. 0d. 1958.

**Stuart-Harris (C. H.)**, and **Hanley (T.).** Chronic bronchitis, emphysema and cor pulmonale. pp. v+252. Bristol: Wright. 42s. 0d. 1957.

**Wallerstein (R. S.), *et al.*** Hospital treatment of alcoholism. pp. x+212. London: Imago. 42s. 0d. 1957.

**Walton (J. N.)**, and **Adams (R. D.).** Polymyositis. pp. x+270. Edinburgh and London: Livingstone. 32s. 6d. 1958.

**Wolman (I. J.).** Laboratory applications in clinical pediatrics. pp. xi+1019. New York, etc.: Blakiston Division of McGraw-Hill. £5 12s. 6d. 1957.

**Woods (G. E.).** Cerebral palsy in childhood. pp. xi+158. Bristol: Wright. 27s. 6d. 1957.

# Inability to take aspirin . . .

IT HAS BEEN reported (*Brit. med. J.*, 1 : 444, 1957) that of 178 rheumatic patients, 25% could not take plain aspirin in adequate dosage.

Of this 25%, however, the great majority tolerated a modified aspirin such as Paynocil.

Not only are Paynocil tablets usually well tolerated by the stomach (even on the heavy dosage needed for rheumatoid arthritis), but they are extremely palatable, disintegrate instantly on the tongue without water, and cause no discomfort or unpleasant after-sensation.

## . . . indicates PAYNOCIL

***non-irritant, palatable, quick-dispersing aspirin***

FOR ADULTS

**PAYNOCIL**

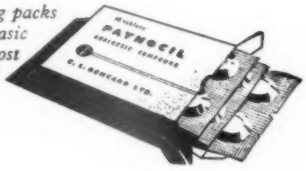
*EACH TABLET CONTAINS*

Acetylsalicylic acid.....10 grains
Aminoacetic acid.....5 grains

*PACKAGES* in sealed foil strips:

*Cartons of 18.*

*Dispensing packs of 240 : basic N.H.S. cost (tax free) 21/8d.*




FOR CHILDREN

**Junior PAYNOCIL**

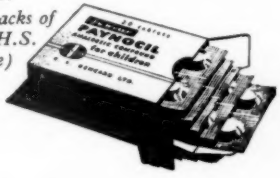
*EACH TABLET CONTAINS*

Acetylsalicylic acid ..... 2½ grains
Aminoacetic acid ..... 1¼ grains

*PACKAGES* in sealed foil strips:

*Cartons of 20.*

*Dispensing packs of 240: basic N.H.S. cost (tax free) 12/-.*




***Detailed recommendations for dosage in rheumatoid arthritis will be gladly supplied on request***

601/65(68)1

**G. L. BENCARD LTD.** PARK ROYAL, LONDON, N.W.10

# THE MOST POWERFUL NITROGEN AND CALCIUM ANABOLIC AGENT

*for both sexes and all ages*

# Durabolin

(NOR-ANDROSTENELONE PHENYL PROPIONATE)

***One 25 mg. injection weekly***

*for*

Inoperable cases of

**MAMMARY CARCINOMA**

with bony secondaries

**OSTEOPOROSIS**

***TISSUE CONSTRUCTION**

***for children 25 mg. fortnightly***

A product of **ORGANON** Research

# Section of Endocrinology

President—T. RUSSELL FRASER, M.D., F.R.C.P., D.P.M.

[*July* 24, 1957]

## The Physiological Control of Aldosterone Secretion [*Abridged*]

By FREDERIC C. BARTTER, M.D.

*National Heart Institute, Bethesda, Md., U.S.A.*

I SHALL not attempt to review all the work that has been done on the control of aldosterone secretion: rather, I shall undertake the much easier task of summarizing our own studies over the past three years.

The method we have used for assay of urinary aldosterone is that of Liddle and associates (1955). This is a bio-assay method, using adrenalectomized dogs on a constant, high sodium diet. The steroid is given intravenously, and the index of activity is a weighed sum of the sodium retention and the potassium loss in the second and third subsequent hours. This index is linear with log-dose over a 32-fold dose range, with a "lambda" for the assay of 0·24. It was shown that cortisone and hydrocortisone, in quantities many times those that could appear in a day's urine, do not materially affect the assay, and so methylene chloride extracts were usually washed but not chromatographed. In the studies with ACTH and cortisone, however, a preliminary extraction with ether was done to remove hydrocortisone.

We have studied the effects of three variables on aldosterone secretion: circulating ACTH, total body potassium, and body fluid volume.

Circulating ACTH was increased by giving large doses of ACTH gel intramuscularly to normal subjects on balance regimens. In all cases aldosterone excretion rose to two to four times control levels. If the ACTH was continued, however, aldosterone excretion fell in a few days to below control levels, and this occurred even when sodium intake was so low as to prevent any retention with ACTH. Circulating ACTH was suppressed with large doses of cortisone and hydrocortisone without appreciable effect on aldosterone excretion. These findings supported observations showing normal aldosterone secretion by patients with hypopituitarism to suggest that ACTH is not necessary, and probably not of great physiological importance, in the control of aldosterone secretion.

Total body potassium was increased by giving large potassium "loads", and decreased by giving low potassium diets, with and without cation exchange resins, to normal subjects on balance regimens. Serum potassium rose and fell with gains and losses of total body potassium in all instances. The potassium "loading" consistently increased aldosterone excretion to about two times control levels, and the potassium depletion consistently decreased it to less than half control levels. The effect of "loading" was present even when extra sodium was given to replace that excreted in response to potassium salts; the effect of depletion was present even on a diet so low in sodium that none could be retained in response to potassium loss.

Despite the consistency of the potassium effects, the relatively small magnitude of the changes in aldosterone secretion despite very large changes in potassium intake suggests that they are not of primary importance in the physiological control of aldosterone secretion.

Changes in body fluid volume were induced experimentally by (*a*) changing total body water volume with dehydration and over-hydration; (*b*) changing extracellular fluid volume with sodium deprivation and sodium "loading"; and (*c*) changing intravascular volume with phlebotomies, and infusion of red cells or of albumin. All subjects were studied under metabolic regimen.

(*a*) *Total body* fluid volume was decreased by depriving normal subjects of water and subjects with diabetes insipidus of pitressin while limiting water intake; aldosterone secretion consistently rose despite moderate to marked hypernatræmia. Total body fluid volume was increased by giving water to normal subjects receiving pitressin tannate in oil to prevent diuresis: aldosterone secretion consistently fell despite marked hyponatræmia.

(*b*) *Extracellular* fluid volume was decreased by depriving normal subjects of sodium, with and without use of mercurial diuretics: aldosterone secretion consistently rose. Volume for volume, the increases in aldosterone secretion were much larger than those induced by deprivation of water alone.

*Extracellular* fluid volume was increased by giving dietary salt or "physiologic" saline infusions to sodium-depleted normal subjects: aldosterone secretion consistently fell. *Extracellular* fluid volume was increased with simultaneous contraction of intracellular fluid volume by infusing hypertonic saline into sodium- and water-depleted normal subjects: aldosterone secretion again consistently fell.

The increase of aldosterone secretion with sodium depletion could be produced during potassium depletion (with falling serum potassium), and the decrease with water or saline "loading" could be produced despite simultaneous potassium "loading" (with rising serum potassium). Thus the "volume" effects were not secondary to effects on potassium metabolism.

(*c*) *Intravascular* volume was decreased by performing phlebotomies on normal subjects, with simultaneous administration of saline to prevent any net sodium loss: aldosterone secretion consistently rose. If several days were then allowed to elapse, aldosterone secretion spontaneously fell as hæmodilution ensued.

*Intravascular* volume was increased by reinfusion of separated red cells into the donors just described: aldosterone secretion consistently fell. *Intravascular* volume was increased by infusion of salt-poor human albumin into normal, hypoproteinæmic, and cirrhotic subjects: aldosterone secretion consistently fell. In the hypoproteinæmic patients, the fall occurred despite large diuresis of sodium and thus *contraction* of *total* extracellular fluid volume.

We have found elevated aldosterone secretion in cardiac, cirrhotic, hypoproteinæmic and nephrotic patients, despite high intakes of sodium and grossly expanded extracellular fluid volume. In all groups except the first, it is likely that intravascular volume is diminished as fluid escapes to the peritoneal cavity or interstitial spaces. In some cardiac patients, increased intravascular volumes have been reported. It may be that "effective" blood volume is compromised in such subjects despite increased total volume. On the other hand, increased aldosterone secretion and increased blood volume have not thus far been reported in the same subject.

The magnitude of the changes in aldosterone secretion with small changes in intravascular volume suggests that "volume" stimuli are of major physiological importance in the control of aldosterone secretion.

## BIBLIOGRAPHY

BARTTER, F. C. (1956) *Metabolism*, **5**, 369.
—— (1957) *Acta med. scand.*, **159**. In press.
——, BIGLIERI, E. G., PRONOVE, P., and DELEA, C. (1957) *In* Aldosterone, International Symposium, Geneva. London.
——, LIDDLE, G. W., DUNCAN, L. E., Jr., BARBER, J. K., and DELEA, C. (1956) *J. clin. Invest.*, **35**, 1306.
DUNCAN, L. E., Jr., LIDDLE, G. W., and BARTTER, F. C. (1956) *J. clin. Invest.*, **35**, 1299.
LIDDLE, G. W., CORNFIELD, J., CASPER, A. G. T., and BARTTER, F. C. (1955) *J. clin. Invest.*, **34**, 1410.
——, DUNCAN, L. E., Jr., and BARTTER, F. C. (1956) *Amer. J. Med.*, **21**, 380.

President—C. N. ARMSTRONG, M.D., F.R.C.P.

[*November* 27, 1957]

**Idiopathic Hypoparathyroidism with Thin Bones.**—H. K. IBBERTSON, M.R.C.P., M.R.A.C.P. and RUSSELL FRASER, M.D., F.R.C.P.

Mrs. M. S., aged 31. Indian.

*History.*—Chronic backache following a fall fifteen years previously. Hysterical attacks with coma and spasms of hands and feet during same period.

Thin bones and macrocytic anæmia discovered during recent (eighth) pregnancy.

*Obstetric history.*—Eight pregnancies:

| | | | |
|---|---|---|---|
| 1942 | Male, stillborn. | 1948 | Male, alive. |
| 1945 | Female, died after fifteen hours. | 1953 | Female, died after ten hours. |
| 1946 | Male, died after few hours. | 1954 | Female, died 1 year pneumonia. |
| 1947 | Male, died after few hours. | 1956 | Female, alive. |

The Wassermann reaction was found to be positive during the 5th pregnancy and a course of penicillin and arsenic given with survival of the child. Despite a negative W.R. the child of the 6th pregnancy died after ten hours.

*On examination* (*three weeks postnatal*).—Thin hysterical Indian woman. Bilateral

lenticular cataracts. Positive Trousseau sign with carpal spasm after application of the cuff for one minute. Bone tenderness.

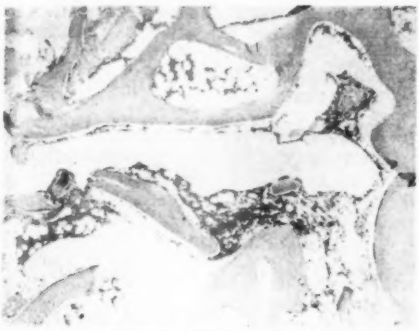


FIG. 1.—Iliac crest biopsy. Decalcified section ×50. H. and E. stain. Shows thin, widely spaced trabeculæ with normal marrow.

*Investigations.*—X-rays: Thin bones. Vertebral wedging. Intact lamina dura. No pseudo-fractures or subperiosteal erosions. Hæmatology: Blood—Hb 11·8 grams/100 ml., M.C.V. 107 cu.$\mu$. W.R. negative. Marrow megaloblastic. Folic acid absorption normal. Biochemistry: Serum calcium 6·2, phosphate 7·3 mg./100 ml. Alkaline phosphatase 5·6 K.A. units. Elsworth Howard Test: Increase in urine phosphate excretion from 10 mg./hour to 60 mg./hour following 200 units parathormone intramuscularly. No rise on control day. Normal result. Strontium infusion test: Daily deposited bone calcium. 0·6 plasma units (low value). Bone biopsy: Thin trabeculæ consistent with osteoporosis. Undecalcified section shows normal osteoid seams.

*Treatment.*—Calciferol 200,000 units daily by mouth. High calcium diet—3 grams of added calcium (as gluconate) daily.

*Progress.*—Restoration of serum biochemistry to normal with relief of bone pain and tetany. Skeletal X-rays unchanged.

*Discussion.*—The association of megaloblastic anæmia with thin bones and tetany suggested steatorrhæa, but two fat balances were normal. The anæmia responded to folic acid and did not return during eighteen months' observation. The clinical picture and therapeutic response was characteristic of megaloblastic anæmia of pregnancy.

The biochemical findings indicated hypoparathyroidism, and the Elsworth Howard test confirmed a normal renal response to parathormone. The occurrence of hypoparathyroidism with thin bones is unusual although demineralization is seen in pseudo-hypoparathyroidism (Reynolds *et al.*, 1952). Albright (1956) described a patient who developed hypoparathyroidism following thyroidectomy. Marked bone rarefaction due to osteomalacia (confirmed histologically) occurred. Rapid healing followed vitamin D therapy. A 12-year-old girl with idiopathic hypoparathyroidism and "demineralized" bones was described by Schulman and Ratner (1955). No histological confirmation was obtained but rapid radiological healing on calciferol therapy suggested osteomalacia.

In the present patient, osteoporosis rather than osteomalacia was confirmed by the characteristic bone histology, a low bone uptake of calcium shown by the strontium tracer test, and absence of radiological change despite correction of the biochemical abnormalities of hypoparathyroidism for eighteen months.

The previous history suggests reasons for the osteoporosis. The diet had been poor and contained little protein or calcium. Lactation was established after each pregnancy, the total duration of lactation being about three years. This, together with the stress of 8 pregnancies, presumably caused depletion of protein and calcium allowing osteoporosis to develop in the presence of hypoparathyroidism.

Whether the so-called "idiopathic" hypoparathyroidism was precipitated in any way by these nutritional factors or whether syphilis itself participated in its ætiology remains speculative.

*Final diagnosis.*—Healed syphilis. Idiopathic hypoparathyroidism. Osteoporosis. Megaloblastic anæmia of pregnancy.

*Comment.*—The plasma calcium and phosphorus and their response to treatment confirm the diagnosis of hypoparathyroidism. The bone biopsy clearly excludes osteomalacia and the bone rarefaction must therefore have been due to osteoporosis. This is a rare association.

## REFERENCES

ALBRIGHT, F. (1956) *J. clin. Endocrin.*, **16**, 419.

REYNOLDS, T. B., JACOBSON, G., EDMONDSON, H. A., MARTIN, H. E., and NELSON, C. H. (1952) *J. clin. Endocrin.*, **12**, 560.

SCHULMAN, J. L., and RATNER, H. (1955) *Pediatrics, Springfield*, **16**, 848.

**Pre-Tibial Myxœdema Following Subtotal Thyroidectomy and Recurring after Surgical Excision.**—J. H. BRIGGS, M.B. (for P. M. F. BISHOP, D.M).

Miss E. S., aged 50.

*History.*—Eleven years ago: Onset of nervousness accompanied by dyspnœa and palpitations on exertion, and considerable weight loss, but her appetite was poor and there was no preference for weather.

*On examination.*—At that time, she had exophthalmos with lid lag, a tremor of the hands which were moist and a tachycardia of 120/min. at rest. B.P. 180/80. B.M.R. +35%. A diagnosis of thyrotoxicosis was made.

Six months after onset of symptoms a subtotal thyroidectomy was performed. Six weeks after the operation swelling of the ankles was first noticed, at first variable and pitting, later persistent and non-pitting—treated with thyroid extract without effect.

Six years ago: Increasing weight, hair falling. B.P. 180/105. B.M.R. +1%. Treated with stilbœstrol implant and later with deep X-ray to the pituitary. There was some regression of the exophthalmos, due possibly to a local effect on the retro-ocular tissue.

Four years ago: A plastic operation was performed, when myxœdematous tissue and skin over the dorsum of the left foot and ankle were excised; a split skin graft from the anterior surface of the left thigh was applied and healed well.

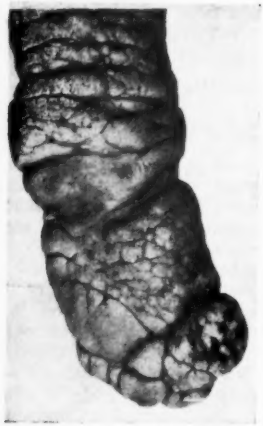


FIG. 1.—Right foot prior to excision of myxœdematous tissue.



FIG. 2.—Three years after plastic operations showing recurrence over both feet and involvement of donor area on left thigh.

Following the operation myxœdematous changes occurred in the donor area on the left thigh; four months post-operatively similar changes took place in the grafted skin on the left foot. Nevertheless the patient was satisfied with the result of the procedure and six months after the first operation, a similar operation was performed on the right foot, skin being taken from the posterior surface of the right thigh (Fig. 1). The grafted skin healed well and although subsequently myxœdematous changes developed in it, in the donor site they did not.

The condition progressed slowly for about two years and is apparently now static (Fig. 2).

X-ray of the hands shows tufting of the distal phalanges. There is no evidence of periosteal reaction over the lower tibiæ or fibulæ.

A trial of tri-iodothyronine ointment applied locally had been ineffective.

The following cases were also shown:

**Exophthalmic Ophthalmoplegia, Treated by Bilateral Orbital Decompression.**—Dr. H. J. WYATT (for Dr. A. W. SPENCE).

**Hypophysectomy by Yttrium 90.**—Dr. G. F. JOPLIN and Professor T. RUSSELL FRASER.

**Acromegaly and Thyrotoxicosis with Pretibial Myxœdema.**—Dr. C. T. DOLLERY and Dr. O. GARROD.

**Riedel's Thyroiditis.**—Dr. A. GRAHAM (for Dr. I. C. GILLILAND).

# Section of Laryngology

President—R. J. CANN, M.S., F.R.C.S.

[*November* 1, 1957]

## Laryngology—A Retrospect, a Review and a Revaluation

### PRESIDENT'S ADDRESS

By R. J. CANN, M.S., F.R.C.S.

BEING curious as to the history of origin of this Section of Laryngology, I discovered that we are this year 50 years old—a golden jubilee—and it seemed a good moment to look back, to take stock of ourselves and, perhaps, to consider the future of our specialty.

1907 was not the beginning of a society of laryngologists in this country, but it was the year when many already existing medical and surgical associations were grouped together to form the Royal Society of Medicine. This Laryngological Section of ours was the amalgamation of two previous existing societies—the British Rhino-Laryngological Association and the London Laryngological Society. The latter was founded by Sir Felix Semon in 1893 and he became its President a year later. While his name is a household one with us, I wonder if we realize just how much, by his writings in this country and in others, by his reputation as a laryngologist and, most of all, by his personality, he helped our specialty to attain recognition and to give it stature. Semon came to London in 1875 as a young man with an introduction to Morell Mackenzie, who was the foremost laryngologist of the country and who, rightly, may be called the founder of Laryngology in this country. It was Mackenzie who started the British Rhino-Laryngological Association in 1888 and was its first President; with Norris Wolfenden a year earlier he had launched the *Journal of Laryngology* and with him shared the editorship. Even more remarkable, in 1863 Mackenzie founded his "Metropolitan Free Dispensary for Diseases of the Throat and Loss of Voice"—the first hospital devoted to diseases of the throat in the world and, of course, better known to most of you as Golden Square Hospital. Laryngology was then a very new branch of medicine and its developing into a specialty may be dated from the discovery of the laryngoscope. Mackenzie had learnt to use the laryngoscope in Budapest from Professor Czermak and within three years of returning to London had won the Jacksonian Prize of the Royal College of Surgeons with his essay on "The Pathology and Treatment of Diseases of the Larynx: the diagnostic indications to include the appearance as seen in the living person".

You will forgive me if I go just one step farther back into history, but on reading Mackenzie's book on the laryngoscope, I discovered one item of particular chronological interest. Much has been written as to who deserves the honour of discovering the laryngoscope and thus of being the founder of our specialty, but there seems little doubt that it was Czermak who recognized its practical usefulness in medicine and popularized it with the medical profession, and it was he who taught Mackenzie. Czermak had borrowed the laryngeal mirrors from Professor Türck of Vienna. Let me quote from Mackenzie's book: "In the year 1857, in the month of November, Professor Czermak, of Pesth, borrowed from Dr. Türck the little mirrors which that gentleman, in spite of the exhortation of his friends, had thrown aside as useless. In a short time, his superior genius, untiring perseverance and natural dexterity, enabled him to overcome all difficulties. Artificial light was substituted for the uncertain rays of the sun; the large ophthalmoscopic mirror of Ruete was used for concentrating the luminous rays; the awkward hinge which united the laryngeal mirror to its stem was dispensed with; and mirrors were made of different sizes. Thus it was that Czermak created the art of laryngoscopy." Did you notice the date?—November 1857. As I have said, this year is a jubilee of our Section—but this month is the centenary of the origin of our specialty.

In looking back I often wonder just what those early laryngologists were like and were able to do. They certainly had the laryngoscope, but they had no electric light, in fact, no electricity for light or cautery or suction. They had no knowledge of bacteria, no X-rays, until 1880 no cocaine and no adrenaline, and they were forced to invent most of their instruments. And yet Mackenzie wrote a textbook on disease of the throat and nose —in two volumes, each of over 500 pages—a work which was a standard for years and which Semon translated for Germany where, also, it had a long reputation. Both of these men were physicians, as were most of the early laryngologists. A notable exception was Sir Henry Butlin who, as junior of the surgeons at St. Bartholomew's, was persuaded to take on the laryngology that no one else was willing to do. Among some who were physicians to their hospitals before they were laryngologists, we remember D. R. Paterson of Cardiff and Watson-Williams of Bristol. Sometimes the apprenticeship was in general practice and notable in this group were Dundas-Grant and Dan McKenzie. But gradually the emphasis in our work became surgical, and the terms of appointment to hospital staff as "Surgeons in Charge" became the custom. More and more the specialty became a branch of surgery with curious anatomical limitations. The possession of a higher qualification in surgery became a necessity for hospital appointments. Also, in many hospitals, we became wedded to the otologists who had been a specialist surgical group for a long time previously. As a result of such a parentage it is now difficult to distinguish a laryngologist from an otologist, and it is perhaps surprising that our Sections of Laryngology and Otology still retain their identity and tradition. I am not, for one moment, suggesting it should be otherwise.

With the development of surgical work, there was a need for larger departments in hospitals with an increasing demand for beds. The supply of beds never seemed to keep pace with this increasing demand and the result was that for many years the waiting lists for throat and nose operations were among the most notorious and most ridiculous features of hospital administration. I think this problem was the cause of two interesting things. One was the development of much out-patient operative work, most of which we should now regard with horror, and the other was the overflow of much of the tonsil and adenoid surgery into the hands of other people, who became expert at this work but were not laryngologists. We are thankful that for one reason and another, the long waiting list is disappearing, or has disappeared.

I suppose I have lived through the heyday of operative assault upon the nose and sinuses and I have seen develop an appreciation of the importance of their physiology. In particular, one has learned the need for the preservation of cilial activity. Otty (1957) reviewed the changing aspect of nasal disease and surgery and commented on the value of a submucous resection of the septum. It may be that this important operation will be one of the few left in our repertoire of nasal surgery. I served some of my apprenticeship at Gray's Inn Road seeing in the out-patient department the "old cases", and among them the anatomical and physiological wreckage of the nose for which nothing more could be done. These were the result of well-intentioned surgery by many well-known seniors, but they caused one furiously to think! Nevertheless, I expect most of my generation still, at times, wish to go the other way and avoid having to look at the all too familiar nose which is waiting on the out-patient benches, pathetically faithful and hopeful, and curiously grateful.

There has been, too, a growing appreciation of the importance of the non-infective disorders of the nose and sinuses, in particular those associated with allergy and those due to psychosomatic changes. Of the latter I have been aware for a number of years but I have been shy of talking or teaching about them. You may remember a lecture by Dr. Lüscher (1954) given at the Institute of Laryngology just four years ago, when he talked of the psychological factors of ear, nose and throat diseases. I talked to him afterwards and thanked him for saying so much of what I believed, and I was interested to hear him say how much courage he had needed to do so. I once thought this type of case was much commoner in private than in hospital practice, but I doubt if this is true. There is more time in private practice to discover them. The discovery must be achieved in hospital practice as well, and achieved by us and not passed on to a specialist in psychological medicine.

While I am one of the few remaining users of the guillotine, I have watched the changing attitude towards the removing of tonsils and adenoids, and I am delighted to see that there now is that "conservation of the lymphoid tissue of the upper respiratory tract" which T. B. Layton, my teacher, so eloquently preached all his life.

I took part in the development of endoscopy. In my early registrar days, the triumph we prayed for was the successful removal of a foreign body from the bronchus. More often we had to rescue a foreign body from the œsophagus—an anxious emergency—each time potentially saving a life. We diagnosed œsophageal malignancy and sometimes stretched

old strictures. At this time the range of endoscopy was widening. I had the good fortune to work with a general surgical registrar who was interested in the possibilities of thoracic surgery and, together, we were officially designated an endoscopic team in our hospital. We quickly demonstrated the value of bronchoscopy in the investigation and treatment of disease of the lungs and we made some elementary efforts at treating or alleviating malignant disease of the bronchi by endoscopic attack. But as soon as surgery of the thorax became as safe as surgery of the abdomen, it seemed inevitable that the endoscopy of the thoracic contents should pass to the thoracic surgeon. In my opinion, we should limit our endoscopic work to the neck. The improvements in general anæsthesia and, later on, the protection imparted by antibiotic drugs, have provided increasing factors of safety in endoscopy. But these particular benefits have been most dramatically of value in the major surgery of the larynx and pharynx. By such means the treatment of malignant disease in this region, by surgery, has reached a degree of success dependent only on the skill of the surgeon and the limits of the disease. Improvements in radiotherapy potential, and technique, are also constantly occurring, and the contest between surgery and radiotherapy in the treatment of malignant disease seems to be more clearly defined—unhampered now by the risks of surgery and the discomforts of radiotherapy.

During the last thirty years, improvements in public health, in housing and in diet for large sections of the community, with especial reference to children, have resulted in less upper respiratory disease, the control of diphtheria, changes in the incidence of tuberculosis and the almost complete disappearance of atrophic rhinitis.

More recently the advent of chemotherapy and antibiotics has started a new era in medicine and surgery, but has been especially forceful in our specialty. In addition to the general benefits, with regard to pyogenic infections, with which our regions can abound, there have been very especial local benefits in tuberculosis and syphilis. These diseases are now rarely seen within the larynx.

In the last ten years or so, some very subtle changes in our work have been occurring as a result of the antibiotic era. The ability to treat and cure acute infections is self-evident, but I refer, rather, to the secondary effect of this curing of acute disease—namely the gradual disappearance of chronic infective and inflammatory changes. This is being revealed now, especially in regard to the lymphoid tissue and in regard to the sinuses. I find in all sections of the community an increasing decline in the numbers of patients needing tonsillectomy or operations on sinuses.

So, where are we to-day? What does the present-day laryngologist do?—or what is there left for him to do?:

He diagnoses and treats—partly surgically—malignant disease in larynx, pharynx and nose.

He treats some acute upper respiratory infections and may have to operate on account of the results of acute infections.

He may need to operate to correct abnormalities of development or injuries toward the general design of a restoration of function.

He has to deal with allergy as manifested in the nose and throat.

He has to discover and deal with psychosomatic illness.

He has to listen to a vast multitude of complaints for which he can find no cause!

Some weeks ago I read that the discoveries of the laryngoscope and of cocaine were important landmarks in the history of our work. I wondered about other landmarks and decided that the establishment of endoscopy was another; then the perfecting of intratracheal anæsthesia exerted a great influence on much of our surgical work, extending the margin of safety and widening the scope. Lastly, the discovery of antibiotics had a very special significance for us. I then dated these landmarks and noticed an interesting sequence. I knew that cocaine was discovered in 1880. Twenty years earlier, 1860 was a fair date for the discovery of the laryngoscope. Twenty years later, 1900 was not far wrong for the endoscopic landmark. Add another twenty and intratracheal anæsthesia was then being more widely used, while 1940 seemed an excellent date for the antibiotic miracle. One is tempted then to wonder what is next on the list? What is put down for 1960? If it is to be an improvement in radiation therapy of malignant disease or some other revolutionary treatment of such disease, then the quota of surgery in the life of a laryngologist is almost gone.

I have always been interested in the teaching of medical students and of newcomers to the specialty. There has been some tendency in recent years for young men already trained in general surgery to consider a further training in laryngology and joining our specialty. We would all agree that this is an excellent sequence, but I do feel it necessary, at present, to ask such trainees why they are wanting to do this—whether they hope they are entering a surgical specialty and warning them that this may not be so.

In our specialty do we continue within the limitations of our predecessors, accepting the occasional amputation of sections of our work and watching the transferring of emphasis from surgical to non-surgical treatment of the majority of our patients? That way, we must again become physicians or even disappear!

Is it right, then, that the emphasis on training and qualification should be surgical? The "Surgeon in Charge" and the "obtaining of higher qualifications in surgery"—are these phrases becoming outmoded? May the laryngologist of the future possess a higher medical qualification?—may he, like Semon, take the M.R.C.P. and become a Fellow of the Royal College of Physicians and not a Fellow of the Royal College of Surgeons? I am being controversial and provocative as I feel we must, for the sake of our young men and women and, therefore, for the sake of the future of this Section, think on these things.

There *are* some sections of surgical work which might be in our province. Some once were—for instance, the thyroid gland—a development from the floor of the pharynx and lying in the middle of our present territory. Who better equipped with instruments and with technique than ourselves for dealing with a cleft palate, and why not the cleft lip with its gap into the nasal cavity? With so much familiarity with the anatomy of the neck, why should we not seek out the sympathetic chain as well? and why should we not regard the tongue and the salivary glands as being within our surgical province?

Morell Mackenzie in November 1888, during his Presidential Address to the British Laryngological and Rhinological Association, said:

> "*I would urgently recommend the younger members of the Association, whilst devoting themselves to our speciality, to continue to practise general medicine or surgery for the first ten years of their professional career.*"

And in the concluding paragraph of the History of Otolarnygology by Scott Stevenson and Douglas Guthrie, 1949, we read:

> "*The great interest of the speciality . . . is that it still contains so many fascinating and stimulating problems for its practitioners, who must not be allowed to forget that they are physicians as well as surgeons and philosophers as well as craftsmen.*"

I work at Guy's in a part of London known still as the Borough—once the home of many Dickens' characters and now the haunt of his ghosts. Monthly, during the winter, we hold a departmental meeting in the one remaining Inn, "The George". A little farther down the High Street is the site of the old Marshalsea debtors prison and, occupying part of it, is the present Southwark Coroner's Court. It is curious how vividly odd remarks made to one stand out in memory.

On my first official visit to that Court, as a house surgeon, I stood in the witness box to testify regarding the post-mortem findings. I do not remember anything about the patient, I only remember the gentle kindly old gentleman, the Coroner, as he asked me my qualifications—M.R.C.S., L.R.C.P.—"Ah yes! a member of the Royal College of Surgeons and a licentiate of the Royal College of Physicians. Ladies and Gentlemen, I would like you to note that the gentleman in the box is both a surgeon and a physician".

## REFERENCES

LÜSCHER, E. (1954) *J. Laryng.*, **68**, 211.
MACKENZIE, M. (1871) The Use of the Laryngoscope. 3rd edition. London.
—— (1888) *J. Laryng.*, **2**, 462.
OTTY, J. H. (1957) *J. Laryng.*, **71**, 257.
STEVENSON, R. S., and GUTHRIE, D. (1949) A History of Otolaryngology. Edinburgh.

[*December* 6, 1957]

A discussion on **Pharyngeal Diverticula** was opened by Professor E. W. WALLS, Mr. F BOYES KORKIS and Mr. M. SPENCER HARRISON. The subsequent speakers included Si VICTOR NEGUS, Mr. W. O. LODGE, Mr. E. D. D. DAVIS and Mr. A. LASKIEWICZ.

This meeting will be published in the *Journal of Laryngology*.

# Section of Medicine

President—W. A. Bourne, M.A., M.D., F.R.C.P.

[*November* 26, 1957]

## DISCUSSION: INTRACRANIAL HÆMORRHAGE—DIAGNOSIS AND TREATMENT

**Dr. P. D. Bedford** (The Cowley Road Hospital, Oxford):

Intracranial hæmorrhage may be arterial, capillary or venous, and its anatomical situation extradural, subdural, subarachnoid, intracerebral or ventricular. The term cerebral hæmorrhage is generally applied to cover all forms of bleeding within the cranium.

Any cause of a general hæmorrhagic tendency may be reflected in bleeding from vessels within the skull, but they are, in addition, peculiarly liable to bleed when no such cause is operative. Although many theories have been advanced to explain this phenomenon, none is satisfactory.

As an expression of the general bleeding tendency, intracranial hæmorrhage may occur incidentally, or as a leading symptom, or as a terminal event in any hæmorrhagic disease—the "primary" and "secondary" thrombocytopenic and non-thrombocytopenic purpuras—whatever the affected element may be, either blood, blood vessels, erythropoietic system, or clotting mechanisms. Thus it is seen in a great variety of general medical disorders as well as in hæmatology. It may also occur in the course of many inflammatory and other diseases of the brain and meninges such as tuberculous, syphilitic and carcinomatous meningitis, Wernicke's encephalopathy and the various encephalitides. Such conditions, however, comprise so small a portion of the whole problem that further consideration of them, although of great theoretical and practical interest, is not warranted here.

Diagnosis is often masked by the gravity of the general illness, and where this is not so, the problems of diagnosis and of treatment are similar to those of spontaneously occurring intracranial hæmorrhage with the exception that specific therapy of the causal condition is in many cases now applicable.

Traumatic cerebral hæmorrhage—whether extradural or elsewhere within the cranium (with the exception of chronic and subacute subdural hæmatoma)—is now virtually the realm of the accident surgeons or of those concerned with the management of the newly born.

Hæmorrhage into intracranial tumours—whether primary or secondary—is an uncommon complication, indeed far less common than is generally realized.

The subjects remaining for discussion therefore are subdural hæmatoma, and spontaneous cerebral hæmorrhage (intracranial and subarachnoid).

### Subdural Hæmatoma

*Diagnosis*

The classical syndrome of subacute or chronic subdural hæmatoma is readily recognizable and sets no further diagnostic problem than the constant and vigilant awareness of its possible occurrence. An injury to the head—which may be severe but is often trivial—is followed after a variable interval by an alteration in the level of consciousness which fluctuates slightly or widely between complete clarity and coma, rapidly or slowly during the twenty-four hours, and is accompanied by focal neurological signs usually comprising pupillary abnormalities and evidence of damage to the pyramidal systems. Indications of cerebral compression later become manifest with ingravescent physical signs and symptoms, and the development of papillœdema. The cerebrospinal fluid (C.S.F.) contains red cells and an increased amount of protein, and the pineal gland—if visible radiologically—is seen to be displaced from the mid-line.

Unfortunately, the very clarity of this classical syndrome has led observers into the catastrophic error of supposing that if the case does not conform to this description in whole or in part, the possibility of a subdural effusion can be dismissed.

But in old age this picture is very much the exception and not the rule; it was manifest in only 1 in 10 of my elderly patients (5 of the 52 cases aged 65 and over, seen by me in the eight years ending June 1957). The condition is known to be frequently atypical in infancy too, but here the ease of exploratory needling before the fontanelles have closed makes the problem of diagnosis somewhat less formidable than in old age. It is supposed that the reasons for these diagnostic difficulties are that the shrinkage in brain volume which

occurs in old age, and the ready elastic expansibility of the cranium in infancy, allows an extravasation of considerable volume to collect in the subdural space before the development of local or general symptoms and signs of cerebral compression. I do not find this explanation entirely satisfying, for firstly, the very old and the very young appear to be quite as intolerant of increased intracranial pressure as those in other age groups, and secondly, I have personally been unable to demonstrate an absolute increase in C.S.F. volume in old age in the absence of large zones of cerebral infarction.

I propose to confine my further observations under this heading to the problem of the diagnosis of *subdural hæmatoma in the elderly*.

Typically the history is that the old person, already somewhat enfeebled, has recently become mentally confused: medical advice or admission to hospital is sought for this latter symptom. A history of a fall within the preceding weeks or months may be elicited—usually by direct questioning—and has been attributed to "old age" or to a "little stroke". The fall may have been accompanied by transient unconsciousness or epileptiform jactitations (and it may be observed here that although a fit is only rarely a symptom of subdural hæmatoma, it is by no means a rare cause of the fall which leads to the blow on the head—trivial or otherwise—which is its almost invariable antecedent). Physical examination only rarely contributes substantially to the diagnosis. The usual clinical picture is that of a mentally confused old person with some impairment of intellectual capacity (which may be slight, moderate or profound), who may be somewhat or deeply drowsy—but is as often not—and who may or may not have bruising about the eyes and forehead: there is often evidence of damage to the pyramidal systems, and occasionally pupillary abnormalities not unjustifiably attributable to ocular disease, which also hinders adequate retinoscopy. Very often, too, concomitant disease of other systems—a fractured neck of femur, bronchopneumonia, heart failure or uræmia—provides further diagnostic distraction.

Manifestly, when the semeiology is classical, the diagnosis is as simple in the elderly as in other age groups; but when the picture I have described is presented, the difficulties are formidable. Indeed, despite the utmost vigilance, only 40% of my elderly cases were diagnosed in life (21 of the 52 aged 65 and over), the others being discovered unexpectedly *post mortem;* for impairment of the intellectual faculties is the rule in old age; falls are a commonplace; an upgoing toe and pupillary abnormalities are common expressions of cerebrospinal and ocular degenerative processes; while mental confusion is an almost invariable accompaniment in old age of diseases anywhere in the body, however remote from the brain. Nor have changing neurological signs or fluctuations in the level of consciousness proved in any way pathognomonic, for hourly records show similar vicissitudes in a wide variety of common geriatric disorders—from uræmia to heart failure—and in other intracranial diseases. Although the C.S.F. protein was elevated (above 90 mg./100 ml.) in 25% of my elderly cases (13 of the 52), and red cells were present in 17% (9 out of 52), any value these observations may have is vitiated by the results of routine lumbar puncture performed on over 4,000 elderly patients, which yielded unaccountably high-protein fluids in no less than 12%. Routine radiography of the skull of all confused patients has proved no more revealing, for displacement of the pineal has been manifest in only 10% of my elderly cases (5 of the 52). It is, however, a valuable sign when it can be demonstrated, but all too frequently the pineal is not visible; and even when it is seen, displacement may not be evident, as was the case in 7 unilateral (13%) and 6 (11%) bilateral subdural extravasations. Even air-encephalography and cerebral angiography have been largely futile, for these examinations cannot be performed as routine on every confused patient—nor indeed on anyone without some very firm indication, which is rarely forthcoming in these cases; while physical frailty, mental confusion and lack of co-operation have led, at best, to only a limited examination being possible and much more usually to the abandonment of the study or to inconclusive results. Electroencephalography (EEG) and investigation with radio-active isotopes have proved valueless; and the only infallible diagnostic measure is exploratory craniotomy. But when it is appreciated that over 80% of more than 5,000 patients aged 65 and over, who were admitted in the past eight years to the Oxford Geriatric Unit, were mentally confused, whatever their salient diagnosis, the size of the problem becomes apparent.

It must reluctantly be admitted, therefore, regarding the diagnosis of subdural hæmatoma in the aged, that unless thousands of old people are to be submitted needlessly to unjustifiable intracranial exploration, every physician concerned in their care will see a number of patients each year in whom the condition unavoidably defies detection; and this unsatisfactory state of affairs is not materially improved by the knowledge that even without surgery these effusions are not invariably lethal.

*Treatment*

Treatment of subdural hæmatoma, when the diagnosis is made, is in the first instance surgical.

## Spontaneous Cerebral Hæmorrhage

This has only recently been the subject of a comprehensive discussion (*Proc. R. Soc. Med.*, 1957, **50**, 281). Physicians and surgeons alike agree that the distinction between primary, subarachnoid and intracerebral hæmorrhage is quite arbitrary—"clinically difficult and often artificial" (Falconer, 1956; Holmes, 1957)—and as I am substantially in agreement with this view, I shall consider these conditions under a common heading.

### *Diagnosis*

Of 5,100 patients admitted to the Geriatric Unit, Cowley Road Hospital, Oxford, in the eight years ending June 1957, there were 63 proven cases of spontaneous cerebral hæmorrhage. My remarks are based largely on these 63 cases but I have also taken into account 55 others seen elsewhere—a total of 118. The condition is commoner in men than in women, by a factor of 1·25 to 1 (35 to 28) for the Cowley Road Hospital series, and 1·8 to 1 in the group seen elsewhere. This greater incidence in males is generally agreed (*see* Wilson, 1955). (Cerebral thrombosis was twenty-one times more common than hæmorrhage in the hospital patients—1,337 to 63 respectively—whereas it was only six times more frequent in those seen elsewhere.) A comparison with Murphy's (1954) figures of 3·25 to 1 and with those of Carter (1957) of 0·7 to 1 forces the conclusion that these are all biased groups and that the true ratio of thrombosis to hæmorrhage is still not known. The diagnosis is often mistaken—as subsequent post-mortem studies have shown—and Wilson's (1955) observation that "the diagnosis (of cerebral hæmorrhage) is still often (erroneously) made for death in old age"—is certainly true.

By far the commonest single associated finding—if not necessarily the cause—of spontaneous cerebral hæmorrhage was hypertension, no less than 80% of all the men and 75% of the women having diastolic pressures of 100 mm.Hg or more. This is in substantial agreement with Russell (1954) who attributed 50% of her 461 necropsy cases of spontaneous intracranial hæmorrhage to hypertensive cerebrovascular disease.

After an exhaustive clinical and post-mortem study of my cases and of the literature, I have little to add to current views and knowledge regarding the diagnosis of spontaneous cerebral hæmorrhage. Some findings which have emerged will be itemized for brevity as random and dogmatic jottings.

(1) Neither old age nor co-existing hypertension should be a bar to the diagnosis of hæmorrhage due to congenital aneurysm. Falconer (1956), Henson (1957), and Rowley *et al.* (1957) have all emphasized that many congenital aneurysms bleed for the first time in old age; while 18 of my cases clearly demonstrate that hypertension and congenital aneurysm are by no means mutually exclusive conditions.

(2) The most important single cause of cerebral hæmorrhage other than that due to trauma, aneurysm, or vascular hamartoma, is degeneration of the media (Turnbull, 1915) of which hypertension is by far the commonest cause, and in which atherosclerosis, although frequently concomitant, plays an uncertain but subsidiary role.

(3) There are no features by which a cerebral hæmorrhage may be predicted in a hypertensive patient—neither "little strokes", nor retinopathy, nor the cause, character or severity of the hypertension: I am here in full agreement with Leishman's (1957) conclusions. There are, furthermore, no apparent features by which the event may be anticipated in the normotensive individual.

(4) Cerebral hæmorrhage is by no means always fatal. I feel that Rose (1948) in his study of post-mortem material paints rather too sombre a picture. I agree with Potter (1956) that "spontaneous recovery to a variable degree may take place, and this may occasionally be assisted beneficially by the surgical evacuation of a clot that is refractory to the natural process of absorption". His statement, however, that "the patient may then survive a year or two . . ." is too pessimistic for I have seen several who have lived for much longer periods.

The commonly-held beliefs that ventricular hæmorrhage is invariably fatal, and that rupture of an intracerebral hæmorrhage into the subarachnoid space relieves the pressure and is therefore of better prognosis, are very frequently erroneous.

(5) As between thrombosis and hæmorrhage, the diagnosis can be impossible in the early, and sometimes in the later stages too. Three reasons for this difficulty are:

*a*) Blood in the C.S.F. is not diagnostic of free hæmorrhage since it has also not rarely been observed in the early stages following thrombotic infarction; while a xanthochromic or high-protein C.S.F. later on is by no means exceptional in the latter.

*b*) Blood may not be found in the C.S.F. in undoubted cases of cerebral hæmorrhage: this has also been emphasized by Rose (1948).

*c*) Even *post mortem* the distinction between cerebral hæmorrhage, and red infarction due to thrombosis, may not be easy, especially as no thrombus is to be found in 60% of

thrombotic cases (Murphy, 1954); and because no cause is to be found in 20% of cases of hæmorrhage (Potter, 1956)—which figure agrees with the 17% in my own series.

(6) The differential diagnosis between subarachnoid bleeding and other intracranial lesions can also be difficult in the early stages. Two reasons for this are:

(*a*) Meningism may be absent in subarachnoid hæmorrhage even in the absence of deep coma, and conversely may be present without blood in the C.S.F. or a C.S.F. pleocytosis. (The former is quite common, of course, in expanding lesions of the posterior cranial fossa and is also not rare in extracranial conditions.)

(*b*) The observation that in subarachnoid hæmorrhage a neutrophil or a lymphocytic pleocytosis without blood in the C.S.F. may occasionally occur (Holmes, 1957) and may lead to the erroneous diagnosis of brain abscess: my own experience confirms this.

(7) The co-existence of other primarily extracranial causes of cerebral symptoms, and signs including papillœdema, can occasionally be a source of great difficulty and may lead on the one hand to the erroneous diagnosis of cerebral hæmorrhage, and on the other to its presence being missed. This difficulty has arisen in my 4 cases of cerebral infarction associated with cor pulmonale (Bedford, 1956), and also in cerebral vascular insufficiency states in patients with malignant hypertension.

(8) In the diagnosis of intracerebral clot, any change whatever in symptomatology or neurological signs following partial or apparently complete recovery from an apoplexy should call attention to its possibility. Serial EEG studies have proved of considerable value in its detection; and air encephalography or cerebral angiography is indicated with a view to surgical evacuation.

(9) Many other investigations, such as the capillary fragility test and examination of the blood for neutrophil leucocytosis or bilirubinæmia, have at one time and another been advocated but are of no specific value in the differential diagnosis of spontaneous cerebral hæmorrhage.

*Treatment*

Consideration of the problems of treatment of intracranial hæmorrhage, whatever its type, situation, or cause, falls under six headings:

(1) Prophylaxis—i.e. the treatment of any predisposing condition.

(2) Prevention of further hæmorrhage.

(3) Evacuation of harmful extravasation of fluid blood or clot.

(4) Management of the unconscious patient in general (the prevention and treatment of bedsores, and of pulmonary, urinary, metabolic, cardiac, oral and bowel complications).

(5) Management of the "cerebral case" in particular—(post-operative and others)—with especial reference to cerebral compression, œdema, and hypoxia; hyperpyrexia; some peculiar metabolic derangements; and agitated mental confusion.

(6) Problems of later management—of such sequelæ as paralysis of function and epilepsy, and of mental confusion, dementia and other psychiatric disorders.

I propose to deal very briefly here with these problems.

(1) The prophylaxis of cerebral hæmorrhage lies essentially in the prevention of by far its commonest cause, namely hypertensive cerebrovascular disease. As the fibrinoid medial degeneration in this condition is probably reversible in its early stages, it is to be hoped that early and effective hypotensive therapy will materially reduce the incidence of cerebral hæmorrhage (Leishman, 1957). The mental confusion of hypertensive cerebrovascular disease—and particularly in the elderly—is almost invariably aggravated by effective hypotensive treatment. It is probable that in these cases the fall in blood pressure produces a state of cerebral vascular insufficiency (Corday *et al.*, 1953) by reducing the blood flow through vessels whose lumen is already irreversibly narrowed (Kety, 1955; Brain, 1956; Millikan *et al.*, 1956).

(2) In the prevention of further hæmorrhage, medicine has little yet to offer. Hæmostatic agents, Filatov's manœuvre, intravenous aminophylline and a host of other treatments have been advocated from time to time but are valueless. Reducing the blood pressure by hypotensive drugs, although theoretically reasonable, has, in my experience, had similarly discouraging results, but possibly the method has not yet been given an adequate trial. Although radiotherapy has been of value in a few of the uncommon cases of hæmorrhage due to angiomatous malformations of the brain, it is to surgery that one must turn for the only small source of proved comfort. Here I would strongly support the bolder approach against the extremely conservative outlook generally prevalent to-day. I agree firmly with Holmes (1957) who states that "surgery should be considered at an early stage in the management of spontaneous intracranial hæmorrhage with the exception of patients who are moribund when admitted to hospital". (I do not agree however with his implication that old age alone should preclude surgical intervention. Indeed, although I am fully alive to the hazards of operation under general anæsthesia in the elderly (Bedford, 1955)

feel strongly that the general approach to surgery in old people is far too timid and is largely irrational to-day having regard to the recent revolutionary advances in anæsthetic skill and techniques. Obviously, although no operation must be undertaken lightly or casually, the one question to be decided—as with the application of all forms of treatment—is the risk of operating as against the chances when operation is withheld; and in this balance the factor of age alone must not be allowed unduly to weight the scales.)

(3) Evacuation of intracranial blood clot is manifestly the province of surgery, and it is only in the less specific spheres of management (listed under headings (4), (5) and (6) above) that medicine has anything reasonable to offer.

(4) A treatise could be written on the problem of bedsores. All I shall mention here is that muscle necrosis almost invariably precedes and is independent of breakdown of the skin: that the "superficial" bedsore, which is simply a cutaneous abrasion, presents no real difficulty: whereas the treatment of a fully developed bedsore is a formidable problem demanding the same level of surgical skill and attention as is given to all grossly infected open lacerated wounds: prevention is the only solution, but frequent turning of maybe several patients makes heavy demands on nursing staff—who would however be better employed on this simple manœuvre than on the time-honoured routine of rubbing, spirit and powder. We have recently been achieving some promising results with an alternating-pressure mattress developed at Cowley Road Hospital, but it is still at an experimental stage.

(5) In the particular management of the "cerebral case" I support with reserve Henson's (1957) rather more enthusiastic and optimistic opinion of the value of hypothermia in cerebral ischæmia, œdema and hypoxia. It certainly, however, merits an extended trial.

My two final observations serve only to raise further problems.

First, (*a*) Peculiar biochemical disturbances are sometimes to be observed following cerebral apoplexy, very similar to those described by Higgins *et al.* (1951, 1954) as following head injury: the mechanism of these disturbances is quite unknown. Only very occasionally has the pattern of pituitary or adreno-cortical derangement, sometimes seen, been rectified by treatment with ACTH or adreno-cortical steroids.

And lastly, (*b*) Mystery, too, shrouds the mechanism and cause of the states of hypermetabolism and of the late renal failure that have sometimes been observed, either consecutively, or quite independently one of the other, to follow an apoplexy. It is possible that the release of large amounts of potassium in this hypermetabolic state may be responsible for some of the cases of renal failure that occur following a stroke.

## REFERENCES


BEDFORD, P. D. (1955) *Lancet*, ii, 259.
—— (1956) *Proc. R. Soc. Med.*, **49**, 614.
BRAIN, R. (1956) *Proc. R. Soc. Med.*, **49**, 164.
CARTER, A. B. (1957) *Quart. J. Med.*, **26**, 335.
CORDAY, E., ROTHENBERG, S. F., and PUTNAM, J. (1953) *Arch. Neurol. Psychiat., Chicago*, **69**, 551.
FALCONER, M. A. (1956) *Proc. R. Soc. Med.*, **49**, 166.
HENSON, R. A. (1957) *Proc. R. Soc. Med.*, **50**, 284.
HIGGINS, G., LEWIN, W., O'BRIEN, J. R. P., and TAYLOR, W. H. (1951) *Lancet*, i, 1295.
——, ——, ——, —— (1954) *Lancet*, i, 61.
HOLMES, J. M. (1957) *Proc. R. Soc. Med.*, **50**, 281.
KETY, S. S. (1955). In: Neurochemistry. Edited by K. A. C. Elliott, I. H. Page and J. H. Quastel. Springfield; p. 294.
LEISHMAN, A. W. D. (1957) *Lancet*, i, 437.
MILLIKAN, C., KETY, S. S., FISHER, C. M., PAGE, I. H., and SAHF, A. (1956) *Neurology*, **6**, 580.
MURPHY, J. P. (1954) Cerebro-vascular Disease. Chicago.
POTTER, J. M. (1956). In: British Surgical Practice, Surgical Progress. Edited by Sir Ernest Rock Carling and Sir James Paterson Ross. London; p. 1.
ROSE, W. M. (1948) *Lancet*, ii, 561.
ROWLEY, J. F., SULLIVAN, J. F., and TUREEN, L. L. (1957) *Neurology*, **7**, 86.
RUSSELL, D. S. (1954) *Proc. R. Soc. Med.*, **47**, 689.
TURNBULL, H. M. (1915) *Quart. J. Med.*, **8**, 201.
WILSON, S. A. K. (1955) In: Neurology. Edited by A. N. Bruce. 2nd edit. London; **3**, 1367.


**D. Reginald Kelly** (London):

I propose to confine my remarks to intracerebral hæmorrhage. It has become clear that there are a number of aspects of this condition which are overlooked both in diagnosis and management of these patients. Kinnier Wilson in his famous textbook of Neurology describes the ictus as follows: "The onset is preceded by warnings in the shape of vertigo, headache, or a sense of oppression for a few minutes. Generally speaking a brief second of bewilderment, a cry as of pain, a vague momentary alarm, or a tragic ejaculation such

as 'Oh! My head' heralds profound and immediate insensibility." As regards the prognosis, he cites Jones (1910) whose figures indicated that out of 109 cases of intracerebral hæmorrhage, death ensued in the first twenty-four hours in 37%, within a week in 72%, within a month in 86% (Wilson, 1940). He states that slight prior seizures are more suggestive of thrombosis than hæmorrhage but a single stroke may occur in either; that more or less definite warning and a certain measurable time for development of symptoms characterise an occlusion, but rarely occur in a hæmorrhage; that loss of senses occurs only when a large area is infarcted but is almost invariable with hæmorrhage; and that the commonest site of hæmorrhage is the internal capsule.

*Treatment*

In most hospitals this is expectant, with physiotherapy for the survivors. The only patients who are referred for surgical treatment are those whose features have led the physician concerned to diagnose either a subarachnoid hæmorrhage or a cerebral tumour, although these are often features which I believe may be characteristic of a cerebral hæmorrhage. Of 34 examples of uncomplicated intracerebral hæmorrhage referred to the neurosurgeons at the Maida Vale Hospital (M.V.H.) the diagnosis of referral was that of subarachnoid hæmorrhage in 15 cases and cerebral tumour in 12.

I have recently been studying the clinical features of all the cases of intracerebral hæmorrhage admitted to St. Thomas' Hospital (S.T.H.) in the past three years—some 34 cases, together with 47 cases of intracerebral hæmorrhage which had been referred for surgical treatment at the M.V.H. Of this latter 47 cases which are of rather highly selected material I have omitted 13 cases which were examples of intracerebral clot complicating a ruptured aneurysm or angioma. I believe that there is no way clinically of deciding whether an intracerebral clot follows the rupture of a diseased or an anomalous vessel, and consequently it seems to me that both types of rupture present the same clinical problem. However, I have omitted these cases because it may well be felt that the behaviour of this particular type of spontaneous bleeding may be entirely different and have a different prognosis.

TABLE I.—CLINICAL FEATURES

| | Gradual | Coma | Headache | Death |
|---|---|---|---|---|
| S. T. H. | 9 | 10 | 14 | 31/34 |
| M. V. H. | 23 | 11 | 15 | 15/31 |

*History* (see Table I)

In the cases which I studied the original ictus was ingravescent in 9 out of the 34 at S.T.H. and in 8 more the patient was, in fact, found either unconscious or incapacitated with no history of how long he had been in that condition or how he had reached it. In only 2 out of the 34 patients did the ictus occur during the night. In the M.V.H. cases 11 of the total had an ictus of sudden onset and the remaining 23 had an ingravescent course lasting from minutes to three days. This greater number in the M.V.H. cases reflects, perhaps, the fact that this was selected material referred to the surgeon as a tumour, particularly because of this ingravescent onset, and in many of them because there had been one or more previous episodes.

*Coma* was apparently by no means a necessary part of the clinical course because only 10 of the S.T.H. cases lost consciousness at the time of the original ictus and only 11 of the M.V.H. cases, in each case less than a third of the total.

*Headache* was recorded from the start in 14 of the S.T.H. cases who were not comatose and in only 15 of the M.V.H. cases. I believe that this low figure may well be due to errors in history taking and partly because many of the conscious patients were aphasic; but even although this is undoubtedly a falsely low figure, it is apparent that headache also is not a necessary factor in the diagnosis.

The history, therefore, is one of a sudden or gradual loss of function over a period of hours to two to three days, sometimes but not always associated with headache. The subsequent course of the illness is one which may well on occasions lead to a suspicion of a tumour. In the majority of cases there is recovery of consciousness with evidence of some brain dysfunction. The condition then remains static for a variable period and finally the patient gradually, occasionally suddenly, deteriorates and dies. The important point as will be readily observed from Table II is that the period of survival after the ictus is

TABLE II.—DURATION OF ILLNESS IN S.T.H. CASES

| | Hours | Days | | | | | | | | | | Weeks | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sudden | 3–12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 | 12 | 2 | 3 | 4 | 5 | 7 | 11 |
| No. of cases | 2 | 2 | 5 | 5 | 0 | 1 | 0 | 1 | 4 | 1 | 1 | 2 | 3 | 2 | 1 | 2 | 1 | 1 |

hours at least, days and even weeks. 18 of our cases survived one or more weeks, and 7 more than three weeks. In these 34 cases untreated by surgical intervention, 31 eventually died and only 3 survived. Of these 3 survivors none had any recovery of function whatsoever.

The following case histories illustrate the ingravescent nature of the onset of many of these cases and the subsequent course of the illness.

*Case I.*—E. P., aged 50, was attending hospital, with pleurisy. While in Out-patients her husband noticed that her mouth was twisted. On the way home she dropped her handbag in the bus and was unable to hold it properly in her left hand. She walked from the bus stop to her home, but on arriving home was unable to walk upstairs because her left leg was gradually becoming weak. This weakness gradually became more severe so that by the time she was admitted to hospital twenty-four hours later she had a left hemiplegia; she was drowsy but rousable. During the course of the next week she gradually drifted into coma. By the end of the week she was in deep coma, and she died seven days after the onset. This illustrates a gradual onset of disability over seven days.

*Case II.*—A. S., aged 63. On getting up the patient complained that she felt queer but had no other symptoms. At midday when shopping, she complained of feeling ill and was said to have stumbled when she walked but she complained of nothing else at the time. That afternoon the kitchen ceiling fell on her, but not on her head; she then went upstairs saying that she felt rather more ill, putting it down to the emotional trauma of losing her ceiling. She lay down on her bed and two hours afterwards she was found to be unrousable. A total period of onset of eight hours.

*Case III.*—H. N. was admitted for surgical treatment of a stricture. On the day after admission he was found unconscious in the toilet, having complained of headache throughout the morning. On examination then he had a right spastic hemiplegia. By the next day his condition had improved. Thirty-six hours afterwards he was rousable. Forty-eight hours after he was conscious, able to speak and to move the paralysed limbs. He continued to improve for eight days. On the eighth day he was obviously confused and within the next thirty-six hours gradually became more dysphasic, incontinent, slipped into coma and eventually died twenty-four hours later. This is an example of the not uncommon story of the sudden loss of consciousness or of function, followed by gradual recovery, a period when the disturbance is static, and finally a gradual deterioration to death. This story I have found may be spread over thirty-six hours, four or five days, or two to three months. Over the whole of this period of three years only one of the many patients who were brought into the Casualty Department of S.T.H. already dead was shown to have died from a cerebral hæmorrhage.

Fits do not appear to be of any diagnostic significance one way or the other since 2 of the S.T.H. and 2 of the M.V.H. series had fits of one sort or another, either at the commencement of the ictus or as a continuing event after the ictus.

TABLE III.—PHYSICAL SIGNS

| | Papillœdema | Meningeal | Blood | Pupils | Hypertension |
|---|---|---|---|---|---|
| S. T. H. | 9 | 15 | 13/14 | 9 | 19 |
| M. V. H. | 10 | 21 | 23 | 9 | 19 |

*Signs which Aid the Diagnosis* (see Table III)

The physician is confronted with a patient who has a focal disturbance of brain function with or without a disturbance of consciousness. Helpful signs in a differentiation from a thrombosis will be the presence of papillœdema, signs of meningeal irritation and the presence of blood in the cerebrospinal fluid, and finally pupillary changes. A greater proportion of these patients will have persistent hypertension and may well have swollen discs as part of their hypertensive retinopathy, although when examined after the ictus the blood pressure is often normal having been reduced by the effect of the hæmorrhage or thrombosis. However, a considerable number of patients with an intracerebral haemorrhage are normotensive, both before and after the ictus. Consequently the absence of a raised blood pressure is no deterrent to the diagnosis. Of the S.T.H. patients the presence of neck stiffness, of a positive Kernig's sign and irritability was recorded in 15 of the 33 cases alive on admission. In the remaining cases no record, either negative or positive, was made of this sign. Papillœdema was noted in 9 cases and its absence in another 5. I think it is reasonable to suppose that both of these physical signs might have been present in one or two more cases. Blood was found in the cerebrospinal fluid in 13 out of the 14 cases in which this examination was carried out.

In the M.V.H. cases 10 patients had papillœdema, roughly the same percentage as the S.T.H. cases. 21 patients, however, had meningeal signs and 23 of the cases had frank blood in their cerebrospinal fluid: a greater number reflecting the selectivity of the material. Indeed it was this combination which obviously led to the diagnosis of a subarachoid hæmorrhage in mistake. It must be clear, however, from these figures that

a sufficient proportion of these cases in both series had neither papillœdema nor meningeal signs to make it apparent that their absence should not lull the physician into a state of confidence that he is dealing with either a cerebral thrombosis or a tumour rather than a hæmorrhage. In a number of cases, either at the commencement or certainly before death, there was either an ipsilateral or later a bilateral pupillary dilatation and fixation: 9 in each series.

TABLE IV.—SITE OF HÆMORRHAGE AT P.M. OR OPERATION

| | Hemisphere | Front. | Temp. | Pariet. | T.O. | Occip. | F.P. | Caps. | Pontine | Cerebellar |
|---|---|---|---|---|---|---|---|---|---|---|
| S.T.H. cases | 14 | | | | | | | 5 | 1 | 3 |
| M.V.H. cases | | 9 | 8 | 2 | 2 | 1 | 3 | 1 | 2 | 1 |

The site of the hæmorrhage found at post-mortem or operation is set out in Table IV. It will be seen that the majority of hæmorrhages in this series are not capsular; that cerebellar and pontine hæmorrhages are not as excessively rare as had hitherto been thought; that the majority of these hæmorrhages occur in situations where it can be expected that irreparable damage has not necessarily been done and that the hæmorrhage is often easily accessible.

*Treatment*

Ever since subarachnoid hæmorrhages have been treated surgically it has often been found necessary to evacuate a cerebral clot. Similarly Jewesbury pointed out (1947) that cerebral hæmorrhage may present as a slowly progressive destructive lesion, mimicking a tumour. The diagnosis in these cases is made only at operation and the hæmorrhage has been evacuated, often with striking recovery. If, therefore, hæmorrhages can be evacuated, as it were by mistake, or during the process of tackling the technically far more difficult task of dealing radically with an aneurysm or an angioma, why cannot an attitude of surgical aggression be adopted towards simple intracerebral hæmorrhage? The only objection would be that the results do not justify the efforts.

We have seen in the preliminary part of this communication that in the untreated group at S.T.H. 31 out of the 34 patients died. 3 recovered consciousness but continued to live with a severe and irrecoverable disability. At the Prince of Wales Hospital over a period of two years 30 patients were admitted with an undoubted cerebral hæmorrhage; of these 30 patients, 6 of those admitted under my care were subsequently operated on. One of these cases died and the remaining 24 all died. Any method of treatment, therefore, which reduces this mortality considerably has surely established itself, particularly if it may result in recovery of function as well. It is against this background of no recovery and of 55 deaths out of 58 untreated cases, with 3 permanently incapacitated people, that the results of a surgical attack must be weighed.

I have personal experience of only 7 cases treated surgically. Of these 7 cases, 1 died on the day after operation and the remaining 6 recovered and were discharged from hospital. The first of these, A. B., recovered from a state of total aphasia and right hemiplegia to a state where his executive speech was normal but he was unable to read, and he had a slight right hemiparesis. He was, however, back at work until a year later when he had a further vascular accident and died. The second patient, D. W., aged 76, had an occipital hæmorrhage evacuated eight years ago at the age of 68 and recovered completely, apart from a left homonymous hemianopia. The third, T. W., aged 56, had an interesting history. Five weeks before he was admitted, there was an attack of vertigo, and a feeling of faintness. An hour later he started to vomit and did so for two days, when it was noted that he had some difficulty in using the appropriate words and he became confused at odd periods. Four weeks later he was admitted to hospital and while there became more irrational and a left hemiparesis gradually developed with papillœdema. On the tenth day after admission there was an epileptic fit, and on recovering consciousness he was completely dysphasic. He remained semi-comatose with a left hemiplegia until he was operated on a week later. A hæmatoma was entered and fragments of clot were sucked out and five days later at craniotomy a large temporal clot cavity was fully evacuated. The cavity stretched 9 cm. from the tip of the temporal horn backwards.

From that point he slowly improved. In spite of the fact that he had such an extensive hæmorrhage, he returned to work nine months after his operation, his only disability being a slowness of thought and action and a mild spastic dysarthria.

The fourth patient, J. L., was aged 54. He had a sudden onset of a right hemiplegia with dysphasia and a large temporal clot was evacuated four days afterwards. He gradually recovered so that by now, eighteen months afterwards, he is living a reasonable social life and can carry out halting, but otherwise almost normal conversation, and is even taking an interest in his business. The fifth patient, A. M., aged 56, presented with a rapid onset of dementia with papillœdema. He steadily went downhill until he was almost comatose. A large frontal hæmorrhage was evacuated and he recovered consciousness but remains moderately demented and disorientated. From his present progress it would appear as though no further recovery can be expected, but

the picture in this case is complicated by his having peri-arteritis nodosa. The sixth patient, A. S., aged 65, presented with a gradual onset of a left hemiplegia; a deep capsular clot was evacuated and she recovered consciousness but has a dense left hemiplegia.

Out of only 7 cases, therefore, already more are alive than out of the 34 untreated cases and some have recovered sufficiently to return to a normal social life. I have not had the time to follow up the cases of my colleagues at M.V.H. to assess their recovery of function, but the immediate results are encouraging.

Out of 34 cases admitted to the M.V.H. and referred to Mr. Valentine Logue for surgery, 31 were treated surgically. 16 of these 31 cases survived to be discharged from hospital and 9 made considerable recovery of function, and 3 more a complete recovery of function. I have not seen these patients but I have only included in these latter patients those in which the notes of the follow-up clinic make it clear that well over 50% of function has returned. In my opinion the contrast between these two sets of figures establishes conclusively the place of surgery in the treatment of intracerebral hæmorrhage.

A number of objections may be raised to suggest that this treatment is for the most part impracticable. It may be argued that the condition is so catastrophic in its effects and the demise so rapid that there is no time to undertake neurosurgical investigations. The figures in Table II indicate that this is certainly not so. It might be argued that the patients are too old for surgery, but the age of these patients is not great: of the S.T.H. patients, 14 were under 60, and 12 under 70. A further objection may be that with severe hypertensive disease one is merely preserving a vegetable just to await further catastrophes. Not only is this not necessarily so with those who are hypertensive, as the histories of my own patients have indicated, but a number of these patients are not hypertensive at all.

It might be argued that the damage caused by the hæmorrhage is so great that no reasonable recovery could be anticipated and that, therefore, the hæmorrhage should be left alone, but these hæmorrhages often do not destroy so much as separate the fibres of the brain and track between them. These hæmorrhages must be relieved to save life because if they remain of any reasonable size inside the brain they eventually act as a growing space-occupying lesion, increasing in size as the weeks go past, causing more damage by compression until eventually the patient dies. Why these hæmorrhages increase in size we have no certainty, but there is evidence that there is an alteration in the type of protein in the fluid remnants of the clot and it seems to be reasonable to suppose that the fluid acts by osmosis in attracting more fluid into the inside of the cyst cavity.

My conclusions then are that cerebral hæmorrhage does not necessarily present with a dramatic onset, loss of consciousness, or headache; in the majority of cases there are signs of meningeal irritation with frank blood in the cerebrospinal fluid; there is a tendency for some recovery after the onset followed by deterioration and finally death in the vast majority and permanently impaired function in the few survivors. Faced with this bad prognosis, the results of surgical treatment are sufficiently good to justify surgical intervention. If the diagnosis is considered in an otherwise fit patient, then he should be investigated by arteriography, followed by craniotomy and complete evacuation of the fluid cavity and the removal of any vascular anomaly. Age is not any bar, the most important factor in deciding about surgical treatment being the patient's previous condition. If there has been no previous gross intellectual deterioration or other disturbance of function, then whatever his age he is certainly unlikely to be damaged but may well be helped considerably by evacuation.

REFERENCES

JEWESBURY, E. C. O. (1947) *Brain*, **70**, 274.
JONES, E. (1910) *Quart. J. Med.*, **3**, 233.
WILSON, S. A. K. (1940) Neurology. London; p. 1070.

**Mr. Lawrence S. Walsh** (London):

The patients with spontaneous intracranial hæmorrhage whom I wish to discuss were all admitted to the Neurosurgical Department of St. George's Hospital and most of them were under the care of Mr. Wylie McKissock. The radiological investigations were performed by Dr. James Bull.

Most of the patients with spontaneous intracranial hæmorrhage that we see have a subarachnoid hæmorrhage and in addition many have a subdural, intracerebral or intraventricular hæmorrhage or a combination of these. The findings in our first 461 cases of subarachnoid hæmorrhage were as follows:

Arterial aneurysms 249 = 54%.
Arteriovenous malformations 53 = 11·5%.
Cerebral and cerebellar hæmorrhages 35 = 7·5%.
No lesion shown 124 = 27%.

In our more recent series—which I shall discuss in this paper—cerebral and cerebell hæmorrhages have formed just over 10% of the cases. I do not think that this represen the true proportion as I am sure many are not referred to us.

Between April 1954 and December 1956 there have been 72 cases of primary cerebr hæmorrhage and 5 of cerebellar hæmorrhage.

72 *patients with a cerebral hæmorrhage.*—Most of these patients had a subarachno hæmorrhage in addition. 4 patients had no evidence of hæmorrhage on lumbar punctu and a few did not have a lumbar puncture performed. Most of them had marked impai ment of consciousness, signs of a cerebral hemisphere lesion and some showed signs tentorial herniation with one or both pupils dilated and non-reactive to light. It is usually difficult or impossible to distinguish this condition on clinical grounds from an intra-cerebral hæmorrhage due to an aneurysm or an angioma. It is our custom, therefore, to perform bilateral carotid arteriography as soon as possible after admission to hospital unless the signs of cerebral compression indicate immediate burrholes. The angiogram may show displacement of vessels indicating an intracerebral hæmatoma which is then aspirated through an appropriate burrhole. In a surprisingly high proportion of cases—just under one-third—no significant displacement is shown. In such a patient with the clinical picture previously mentioned we then make post-parietal burrholes and an intra-cerebral hæmatoma is often encountered and aspirated. If not, a ventriculogram is performed, the hæmatoma localized and aspirated through an appropriate burrhole. I would thus like to stress the value of burrholes, with additional ventriculography if indicated, in showing the presence of, and localizing an intracerebral hæmatoma in the presence of a normal arteriogram.

This is exemplified by the following case:

A man of 49 who was hypertensive, had, four days before admission, complained of a sudden severe headache, become comatose and developed a left hemiplegia. Lumbar puncture showed blood-stained C.S.F. The arteriogram was normal.

A ventriculogram was performed and this showed a large hæmatoma cavity in communication with the ventricle in the right frontal region and this was evacuated through a frontal craniotomy but he subsequently died. Post-mortem examination showed the hæmatoma cavity extended downwards into the internal capsule.

This is an unusual situation for a primary intracerebral hæmorrhage. Most of them are in the temporoparietal region, tending to split the white matter just lateral to the ventricle and communicating with the ventricle in the region of the trigone. In some the hæmatoma seems mainly in the thalamus having ruptured upwards into the ventricle and in these latter the chances of successful removal are very slight. This splitting of the white matter mentioned above means that some cerebral tissue may be compressed and not destroyed, so that removal of the hæmatoma may allow of considerable recovery.

Having aspirated the hæmatoma through a burrhole the usual procedure is to perform a craniotomy a few days later when a considerable amount of solid hæmatoma is evacuated and the interior of the cavity inspected. In an appreciable proportion of these patients a vascular abnormality is seen—one which has not been shown by angiography—and dealt with. Occasionally a biopsy taken from the hæmatoma wall has shown histologically the features of an angioma when no abnormality could be seen macroscopically. Still more rarely a small angioma has been found at post-mortem examination when no vascular abnormality was found at operation.

The next two cases illustrate this point.

A male aged 25, who was not hypertensive, had had a subarachnoid hæmorrhage one week before admission to hospital and since then had remained comatose with a left hemiplegia. Bilateral carotid arteriography showed that the anterior cerebral arteries were displaced to the left. The ventriculogram showed a cavity in the right frontal region communicating with the ventricles. A craniotomy was performed and an intracerebral hæmatoma was evacuated. A large thrombosed aneurysm 3 × 2 cm. in size was revealed, arising from the termination of the right internal carotid artery. This was packed and the patient made a good recovery.

A hypertensive female, aged 50, had suddenly become unconscious twenty-four hours before admission to hospital. Lumbar puncture showed blood-stained C.S.F. Bilateral carotid arteriography showed displacement of the anterior cerebral arteries to the right but no vascular abnormality. A left frontal burrhole was made and a hæmatoma aspirated. Later a frontal craniotomy was performed and the hæmatoma evacuated. A small fragment of abnormal tissue was removed and on histological examination this proved to be an angioma.

These 3 cases then exemplify two important points in diagnosis. Firstly that a large hæmatoma may be present with little or no displacement on the arteriogram and second that a vascular abnormality may be present which is not revealed by arteriography.

To return now to the 72 patients with a primary cerebral hæmorrhage. In these

vascular abnormality was shown by arteriogram, operation or post-mortem examination. Most, but not all, of them were hypertensive and the commonest age group was between 51–60 years.

The results in these patients were as follows:

18 were not treated surgically—15 deteriorating and dying before treatment could be carried out. The other 3 were improving and surgical treatment was not thought to be indicated.

54 were operated on, the hæmatoma being evacuated through a burrhole or at craniotomy. Of these 24 died shortly after operation, 2 of other causes.

4 were discharged unchanged and died weeks or months later.

2 were improved and died later of other causes.

4 were improved and died later of a recurrence of intracranial hæmorrhage—in one, at least, it was known to be in the opposite hemisphere.

20 patients survive and of these 10 are well and 10 are more or less disabled.

As one might expect it is the younger patient, with lower blood pressure and less marked neurological signs who does best and it is especially those who have survived some days after the initial attack and whose downward course has been slow who have made the best recovery.

## Cerebellar Hæmorrhage

In this series there were 5 patients who had a primary cerebellar hæmorrhage. 4 of these died and 1 survived.

3 of the 4 patients who died did so before their investigations were complete, one of them from perforation of a chronic duodenal ulcer. The fourth, a man of 70, died three weeks after posterior fossa craniotomy.

The patient who survived was a hypertensive woman of 63 who had a large hæmatoma evacuated from the left cerebellar hemisphere over a year ago and who is now well.

In the past two or three months we have seen at least 6 patients with a primary cerebellar hæmorrhage or with a hæmorrhagic infarct in one cerebellar hemisphere. It may be that this increased incidence is chance or that we are now detecting these cases more frequently.

These patients are usually hypertensive and they show a marked impairment of consciousness. If they are able to speak at all their speech may be unintelligible and this disturbance of speech may be mistaken for dysphasia. There is sometimes a clue to the diagnosis in the history or on examination but often a supratentorial lesion may be suspected.

Bilateral carotid arteriography shows no vascular abnormality but may show widely swept anterior cerebral arteries suggesting hydrocephalus. In the few patients in whom we have performed a vertebral arteriogram it has not been helpful.

Air ventriculography may or may not show dilated lateral ventricles and if the fourth ventricle is filled—by Myodil if necessary—it shows the typical displacement of a cerebellar space-occupying lesion with sometimes an irregular filling defect in the fourth ventricle indicating the presence of hæmatoma.

The treatment is to perform a posterior fossa craniotomy and remove the hæmatoma or hæmorrhagic infarct.

The following 2 cases illustrate some of the features mentioned above:

A hypertensive female aged 48 had, two days before admission, developed a severe headache and became very drowsy. She had a right hemiparesis. Lumbar puncture showed slightly blood-stained xanthochromic C.S.F. Bilateral carotid arteriography showed no abnormality. Ventriculography was performed and this showed a space-occupying lesion in the left cerebellar hemisphere. A posterior fossa craniotomy was performed and the lower, lateral part of the left cerebellar hemisphere was necrotic, congested and infarcted. This was removed and the patient showed a steady improvement after operation.

A 63-year-old, hypertensive female collapsed twenty-four hours before admission to hospital and complained of severe headache. She was drowsy and had a speech disturbance which was thought to be dysphasia. She had a right-sided hemiparesis, which fluctuated considerably, and bilateral extensor plantar responses. Bilateral carotid and vertebral arteriography showed no abnormality. Ventriculography with air showed dilated lateral ventricles but the fourth ventricle could not be seen. A Myodil ventriculogram showed displacement of the fourth ventricle indicating a space-occupying lesion in the right cerebellar hemisphere. At operation a hæmatoma was evacuated from the right cerebellar hemisphere. The patient improved after operation.

In conclusion then I would say that although the percentage of success in treating primary intracerebral hæmatoma is small, surgery has a definite, though probably limited, place in the treatment of these patients.

The patient with a massive hæmorrhage and rapid downward course is unlikely to be helped but those whose condition deteriorates more slowly seem suitable for surgery and sometimes the improvement in their signs is dramatic following evacuation of the hæmatoma.

## BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

**Biegański (W.).** Myśli i aforyzmy o etcye lekarskiej. (Polskie Toearzystwo Historii Medycyny, Teksty nr. 1.) 4th edit. pp. 164. Warsaw: Państwowy Zakład Wydawnictw Lek. 1957.

**Borstel.** Tuberkulose-Forschungsinstitut. (Institut für experimentelle Biologie und Medizin.) Jahresbericht, 1954–55. pp. 692. Berlin, etc.: Springer. DM. 83. 1956.

**Brugsch (H.).** Vergiftungen im Kindesalter. pp. 222. Stuttgart: Enke. DM. 25.50. 1956.

**Buerger (M. T. F.).** Einführung in die pathologische Physiologie. 5th edit. pp. 652. Stuttgart: Thieme. 1956.

**Catel (W.).** Die Pflege des gesunden und des kranken Kindes. Zugleich ein Lehrbuch der Ausbildung zur Säuglings- und Kinderkrankenschwester. 5th edit. pp. 655. Stuttgart: Thieme. DM. 42. 1956.

**Erichsen (J. E.).** On concussion of the spine, nervous shock and other obscure injuries of the nervous system in their clinical and medico-legal aspects. pp. 340. London: Longmans. 1875.

**Falcão (E. de C.).** Novas achegas ao estudo da determinaçáo da especificidade do "Schistosomum mansoni". pp. 211. São Paulo. 1957.

**Fraga de Azevedo (J.),** and **Murtinheira de Medeiros (L. do C.).** Os moluscos de água doce do ultramar português. II. Moluscos do sul do save (Mocambique). pp. 116. Lisbon. 1957.

**Hanley (H. G.).** Recent advances in urology. pp. 270. London: Churchill. 1957.

**Heisenberg (W.).** Nuclear physics. Translated by F. Gaynor and A. von Zeppelin with the assistance of W. Wilson. pp. 225. London: Methuen. 1953.

**Horler (A. R.).** The hereditary hæmorrhagic disorders. (Thesis for Doctor of Medicine, Durham University.) Typescript. 1955.

**Institute of Medicine of Chicago.** Terminal care of cancer patients. pp. 211. Chicago. 1950.

**Klose (H.).** Arzt, Natur und Kunst. (Sammlung zwangloser Abhandlungen aus dem Gebiete der Chirurgie, Heft 6.) Halle: Carl Marhold. DM. 8.70. 1955.

**Lemierre (A.).** Un grand médecin français: Widal. pp. 146. Paris: Expansion Scientifique Française. 1955.

**Mackey (H. O.).** A handbook of diseases of skin. 5th edit. pp. 261. London: Macmillan. Dublin: Fallon. 8s. 6d. 1956.

**Meerloo (J. A. M.).** Mental seduction and menticide: the psychology of thought control and menticide. pp. 324. London: Cape. 21s. 0d. 1957.

**Munk (F.).** Das medizinische Berlin um die Jahrhundertwende. Hrsg. von Klaus Munk. pp. 183. Munich and Berlin: Urban u. Schwarzenberg. DM. 16. 1956.

**Nichans (P.).** Hypertrophie des glandes paraprostatiques et cancer de la prostate: brève vue d'ensemble. pp. 20. Berne: Huber. 1948.

**Peters (J. A.).** Manipulation: (or massage). pp. 159. Newcastle-on-Tyne: Longhurst. 1901.

**Roger (H.),** and **Poursines (Y.).** Les méningo-neurobrucelloses. pp. 248. Paris: Masson. 1938.

**Rooseboom (M.).** Microscopium. pp. 59. Leiden: Rijksmuseum voor de Geschiedenis der Natuurwetenschappen. 1956.

**Roques (F. W.),** ed. Diseases of women. 9th edit. pp. 480. London: Arnold. 28s. 0d. 1953.

**Seward (C. M.).** Bedside diagnosis. 4th edit. pp. 430. Edinburgh and London: Livingstone. 21s. 0d. 1957.

**Sociedad Española para el Estudio de la Esterilidad.** Actas. Vols. 1–3, 1953–1955. Madrid: Soc. Esp. Estud. Esterilidad. 1954–55.

**Taylor (A. G. C.).** Radical or local mastectomy and radiotherapy. pp. 11. Southampton: Royal South Hants Hospital. 1957. (two copies).

**Vondra (J.),** and **Bláha (R.).** Verletzungen der Schädelknochen: ein Atlas der klinischen und röntgenologischen Diagnostik. pp. 316. Prague and Berlin: Artia & Verlag Volk u. Gesundheit. DM. 24. 1957.

**Williams (R. R.).** Williams-Waterman Fund for the combat of dietary diseases: a history of the period 1935 through 1955. pp. 120. New York: Research Ass. 1956.

## BOOK REVIEWS

**Medical Treatment.** By Kenneth MacLean, M.A., M.D., F.R.C.P. (Pp. vii + 696; 50s. 0d.) London: Churchill Ltd. 1957.

This new book on Medical Treatment, written entirely by Dr. Kenneth MacLean except for the chapters on Tropical Diseases, has the very real advantage of uniformity of style and approach to therapeutic problems. It has inevitably, by the same token, the disadvantage that the more specialized sections cannot have that stamp of authority which the expert alone can give. The methods advocated, however, are for the most part clearly given, with balance and the weight of experience, and, together with the descriptions of medical manœuvres with needles, are of sufficient detail to be of real practical value.

The details of treatments are usually preceded by brief descriptions of the problems they are designed to alleviate, or by a discussion of underlying principles, as, for instance, in the chapter on "Fluid and Electrolyte Disturbances", a subject which bristles with difficulty in presentation. There are also useful chapters dealing with treatment by steroid hormones and antibacterial agents, thus avoiding much repetition in the text.

Any reviewer can always find minor points on which he differs from the author. It would seem, for instance, that whilst emphasis is rightly placed on the dangers attendant upon oxygen therapy in patients with cor pulmonale, sufficient weight is not given to its value in that condition. There also seems to be quite a lot of, if not dead, at least dying wood, the morbid state of which is usually duly recognized by the author himself and will doubtless come under the pruning knife in subsequent editions. There is, nevertheless, no lack of the new in therapeutics, and this book is an up-to-date one.

He is a brave man who is willing to edit a book devoted to medical treatment as the task is immense and recurring, and for the courage of a practising physician who writes all himself amazement at his energy can only be surpassed by admiration for his achievement.

**Atlas of Systematic Human Anatomy.** By Gerhard Wolf-Heidegger, M.D., Ph.D. Volume 3. Systema Nervorum—Vasa Sanguinea et Lymphacea. Foreword by G. A. G. Mitchell, O.B.E., T.D., M.B., Ch.M., D.Sc. (Pp. 167; 172 plates; 55s.) Edinburgh and London: E. & S. Livingstone. 1957.

To quote from the foreword by Professor G. A. G. Mitchell "The present volume, like the first, is an outstanding production and is characterized by its wide scope and beautiful drawings". Your reviewer can whole-heartedly endorse this statement.

The atlas contains 172 illustrations of which 160 deal with the central and peripheral nervous system. The illustrations are based on dissections which were specially prepared for this purpose. These were supplemented by other preparations in the Basle Anatomical Institute.

In order to make many of the illustrations in the central nervous system as true and exact as possible and to avoid disturbing their artistic beauty by pointers lines, a corresponding line drawing appears on the adjacent page. As the Parisian Nomina Anatomica of 1955 are now recognized internationally they have been, with few exceptions, used in the atlas.

The author, artists and publishers are to be congratulated for producing such a fine atlas. It can be recommended without reservation.

**Inhalation Analgesia in Childbirth.** By E. H. Seward, M.A., D.M.Oxon., F.F.A. R.C.S., D.Obst.R.C.O.G., and R. Bryce-Smith, M.A., D.M.Oxon., F.F.A. R.C.S. (Pp. viii +58; illustrated; 7s. 6d.) Oxford: Blackwell Scientific Publications. 1957.

For relieving the pains of childbirth, inhalational analgesia is but one of the many available techniques, not one of which can be guaranteed to be completely satisfactory in every case. It is, however, safe, relatively simple, and, if administered with understanding and attention to detail, as effective as any other method; moreover for the unsupervised midwife its scope has recently been enhanced by the introduction of approved inhalers for Trilene as an alternative to the long-established nitrous oxide.

Besides comparing the merits of these two drugs and describing the apparatus available for their administration, this little book admirably expounds the principles of inhalational analgesia and gives clear instructions for obtaining the best results.

Although written primarily as a practical manual for midwives, for whom it can be strongly recommended, it could also be read with advantage by anyone concerned with the management of labour, including many expectant mothers.

The book is well produced with an excellent index, while appendices give the specification for trilene inhalers as laid down by the Medical Research Council, together with extracts of the rules of the Central Midwives Board which are relevant to their use.

There are two minor misprints.

**An Annotated Bibliography of the History of Medicine in Australia.** By Bryan Gandevia, M.D.Melbourne, M.R.A.C.P. Foreword by Sir Gordon Gordon-Taylor, K.B.E., C.B., F.R.C.S. pp. 140; £A1 15s. Sydney: Australasian Medical Publishing Co. Ltd. 1957.

Bibliographies are useful for reference, but often make dull reading. In this scholarly bibliography—obviously a labour of love—compiled by the Hon. Curator of the Medical History Museum, Medical Society of Victoria, Melbourne, the succinct and stimulating annotations considerably enliven the text and often whet one's appetite for reading the original articles. The material is divided into 18 sections which include medical aspects of the discovery and exploration of Australia; medical aspects of England–Australia transport; early colonial medical practice; history of specific diseases in Australia; medical institutions and organizations; biography and autobiography; the Australian contribution to medical and allied sciences; medical journalism; aboriginal medicine. The author's abbreviations of journals are entirely his own, and it is regretted that in the case of articles the inclusive pagination has not been given. The index of personal names and subjects is a model. The price of the book can only be described as a tragedy, for it deserves the widest possible circulation.

**Lumbar Puncture and Spinal Analgesia.** By Sir Robert Macintosh, M.A., D.M., F.R.C.S.Ed., F.F.A. R.C.S. 2nd edit. (Pp. viii + 142; illustrated. 25s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

Only very minor alterations, chiefly in the references, have been made for the second edition of this now celebrated monograph.

Concise text and excellent illustrations combine to give a lucid description of the relevant anatomy and of the technique of lumbar puncture; while the basic principles of spinal analgesia are clearly expounded with a refreshing absence of the emotional bias which this subject so often engenders.

Due weight is given to the management of the immediate circulatory and respiratory disturbances associated with subarachnoid block, while for the prevention of neurological complications, great stress is rightly laid on the importance of a strict aseptic technique using autoclaved equipment and drugs; though a list of those drugs able to withstand this treatment could be included with advantage.

There is an excellent chapter on headache, but some disappointment may be felt that the later and more serious sequelæ of spinal analgesia are not considered in greater detail, as the fear of these complications still deters many workers from employing this valuable technique.

This well-produced and stimulating little work, which does not claim to be a textbook, can be highly recommended for the houseman about to perform his first lumbar puncture, for all surgeons interested in spinal analgesia, and for every anæsthetist.

**British Pharmaceutical Codex 1954 Supplement 1957.** Published by direction of the Council of the Pharmaceutical Society of Great Britain. (Pp. xiii + 124. £1 7s. 6d.) London: The Pharmaceutical Press. 1957.

Compiled by the Codex Revision Committee of the Pharmaceutical Society, assisted by a number of subcommittees, this Supplement contains 44 new monographs in Part I (among others Chlorpromazine Hydrochloride, Corticotrophin, Hydrocortisone, Prednisolone, &c., and Reserpine) and several amendments which have been published in the *Pharmaceutical Journal* since the British Pharmaceutical Codex was issued. Appendixes (it is refreshing to find this word spelled correctly) describe assay methods for Erythromycin, Hyaluronidase, Phenoxymethyl-penicillin, Polymyxin B sulphate, Injection of Protamine Sulphate and Tetracycline Hydrochloride. This indispensable work of reference concludes with a careful index.

**Simulium and Onchocerciasis in the Northern Territories of the Gold Coast.** By G. Crisp, B.Sc., Ph.D., F.Z.S., F.R.E.S. (Pp. xvi + 171; illustrated. £2 17s. 6d.) London: H. K. Lewis & Co., Ltd., for the British Empire Society for the Blind. 1956.

Dr. Crisp has produced an excellent account of onchocerciasis in the Gold Coast or Ghana, as it has now become. It is based on his work, initiated by the British Empire Society for the Blind, carried out from 1952–55 in the northern territories of the country where half a million of the inhabitants suffer from the disease and about 30,000 are blind. The largest part of the monograph is devoted to the insect vector of the disease, named *Simulium damnosum*. The exact distribution of this fly is described in detail and this information will prove invaluable for future workers in the territory.

Interesting new data on the bionomics of adult *S. damnosum* are reported. The females were found to bite cattle in very large numbers, 110 flies being caught in a hour on one occasion biting the belly of an ox. The extent to which the fly is zoophilic probably varies

[*Continued on p. 22*]

# *Recent Titles in the Modern Trends Series*

## MODERN TRENDS IN GASTRO-ENTEROLOGY—*Second Series*

Edited by F. AVERY JONES, M.D., F.R.C.P. Pp. xviii+417+Index. 153 illustrations. 78s. 6d. net by post 2s. extra.

This second volume in the series is the joint work of physicians and surgeons, anatomists and radiologists who concentrate attention on the many advances achieved in the past five years, relating them to particular diseases, new methods of investigation and the latest therapeutic knowledge.

## MODERN TRENDS IN ENDOCRINOLOGY

Edited by HAROLD GARDINER-HILL, M.D., F.R.C.P. Pp. ix+298+Index. 16 illustrations. 65s. net, by post 1s. 9d. extra.

This new book covers the results of the vast amount of research which has gone into endocrinology over the past ten years, presenting the broadest outlook and emphasizing the modern approach.

## MODERN TRENDS IN GERIATRICS

Edited by WILLIAM HOBSON, B.Sc., M.D., D.P.H. Pp. viii+407+Index. 68 illustrations. 72s. 6d. net, by post 1s. 9d. extra.

The lengthening of the life span has brought about a new awareness regarding the care of the elderly, and this new book makes a timely appearance, for it presents the results of much recent research on both sides of the Atlantic. Nutrition, psychology, skin and respiratory conditions, orthopaedics, hospital care, gynaecological and surgical problems are among the many subjects reviewed.

## MODERN TRENDS IN NEUROLOGY—*Second Series*

Edited by DENIS WILLIAMS, C.B.E., M.D., D.Sc., F.R.C.P. Pp. xi+350+Index. 80 illustrations. 72s. 6d. net, by post 1s. 9d. extra.

The title *Modern Trends* has been followed literally in this Second Series and each section is of marked contemporary interest. A number of chapters are directly concerned with anatomy, physiology and pathology, and since as many are written by surgeons or pathologists as by physicians, this up-to-date book will have a very wide appeal.

## MODERN TRENDS IN BLOOD DISEASES

Edited by JOHN F. WILKINSON, M.D., M.Sc., Ph.D., F.R.C.P., F.R.I.C. Pp. vi+341+Index. 92 illustrations. 2 colour plates. 65s. net, by post 1s. 9d. extra.

". . . to be recommended to general physicians and pathologists wishing to keep abreast with this rapidly advancing branch of medicine. Moreover, the expert hæmatologist will find it a convenient source of information on subjects outside his own special fields."—*The Practitioner.*

**BUTTERWORTHS :: 88 KINGSWAY :: LONDON, W.C.2**

**Showroom : 11-12 BELL YARD, TEMPLE BAR, LONDON, W.C.2**

## THE TUDOR GOVERNESS



Katherine Champernowne, the daughter of a knight, was appointed governess to the Princess Elizabeth in 1536, when the latter was about three; and as was the custom in those days, she also took control of her household. In 1545, Katherine married a son of John Astley who was first cousin to the ill-fated Anne Boleyn. After the death of Henry VIII, she was imprisoned in the Tower on a charge of high treason, but was released when her Royal Pupil championed her cause. Elizabeth, it is said, was far more bound by affection to her Governess than to any parent.

There are many men and women today whose affection and respect for an old governess is very great, and if they cannot themselves make provision for her she can turn to the **G.B.I.** for help.

## GOVERNESSES' BENEVOLENT INSTITUTION

(*for the benefit of Governesses and private teachers*)
58 VICTORIA STREET, LONDON, S.W.1

from region to region and the degree of variation may constitute an important epidemiological factor. Artificial feeding of adults could only be obtained if large cages were erected over the breeding places and baited animals were introduced during the following days. Flight range and longevity were studied and gave maximum figures of 12 miles and two months respectively. There is an interesting discussion on dry season survival of the insect and it was shown that aestivation probably occurs in *S. damnosum*.

The larval behaviour of *S. damnosum* was studied in even greater detail and many new observations were made. The excellent photographs of breeding places of *Simulium* and the general countryside show very clearly the characteristics of infested regions in Ghana. An interesting feature is the absence of trees in many of the worst districts.

A brief account is given of the incidence of *Onchocerca volvulus* in the fly and in man, while the possibility of an animal reservoir is considered but largely discarded.

The final part of the book is devoted to methods of control of onchocerciasis with particular reference on an attack on the vector. A control plan based on larvicidal treatment of infested rivers is suggested for the elimination of the disease from the most highly infested regions of the country.

**The Epidemiology and Control of Malaria.** By George Macdonald, C.M.G., M.D., F.R.C.P. (Pp. xiv + 201 + xl + 11; illustrated; 30s.) London: Oxford University Press. 1957.

This well-planned book makes a mathematical approach to the problems of malaria to explain the very different pictures presented by this disease in Africa, India, Malaya and other endemic areas.

After touching on the earlier studies of malarial epidemiology through its circumstantial period (up to 1850), the later ætiological development (to 1900) and the more recent biological advances, the author follows numerically the various factors affecting transmission, and suggests that not only is mathematical epidemiology the most important branch of the science, but the only possible means of integrating the remaining data into a completed whole.

In a series of concise chapters, he considers the stages of the parasite in both man and mosquito, analysing in turn all the variables involved. The mean duration of parasitæmia in man, its reciprocal as modified by the proportionate infectivity to mosquitoes, superinfection and its effect on the build up of a heterologous immunity as found with *P. vivax* and *P. falciparum*, the longevity of the vector, its man-biting habits and even the susceptibility of the anopheline to species and strain of parasite are all given mathematical expression.

The reproductive rate is calculated from the chances of survival of the mosquito, its frequency of feeding and the availability of the preferred host. This in turn is modified by the development of immunity in the population and superinfection in man and mosquito, so that one perceives a critical level below which the disease decreases indefinitely.

Sporozoite and parasite rates, dependent on each other, are discussed in connexion with the onset of epidemics, upon which the effect of the differing incubation intervals are stressed. During the epidemic the parasite rate rises to achieve, when immunity sets in, a plateau of equilibrium. But the height of this plateau depends largely on the reproductive rate locally, in that the more often the chance occurs of man being bitten, the more stable the epidemiological condition with less variation from the mean.

The parasite density in age groups and the frequency of parasitæmia is shown to reflect the intensity of infection, and it is pointed out that heavy gametocytæmia is largely restricted to the younger children, reduction occurring after the first year. Restriction to even younger age groups is found if transmission for any reason is suddenly increased; this tends to restore the equilibrium and explains the absence of epidemics in highly endemic regions.

In areas of "unstable" or irregular malaria, no such limitation of susceptibility to the youngest is seen; and many grow up without resistance. Epidemics may then occur suddenly and violently, only to end when immunity develops and gametocytes are restricted.

The author confirms, by a careful examination of data from areas where endemic malaria can be categorized as stable or unstable, that with high transmission the human infection rate shows slight response to changes in the transmission factors, but varies greatly when the normal transmission is low. The species of parasite and the habits of the anopheline in those areas conform to what might be expected.

The distribution of malaria throughout the world is discussed with an outline of the epidemiology in each of the twelve regions. Rightly the attention of the reader is directed elsewhere for more detailed studies.

Malaria control is shown to require a considerable degree of local knowledge of vector habits and rural housing before an effective programme can be drawn up. This is a most useful chapter.

Drugs now in use and their action on parasite and patient are fully described, and their varying effect upon the different strains of parasite and upon patients with different degrees of immunity is stressed.

Imagocidal and Larvicidal programmes are well discussed though the somewhat dogmatic choice of D.D.T. in oil as the best larvicide in all circumstances is open to question. The mechanisms of control, chemical biological and mechanical, are touched on briefly, and it is regrettable that limited space forbade a more detailed account of common breeding places and the larvicide of choice in each case.

Records of anopheline resistance to insecticides are well covered and the division of chlorinated hydrocarbons into two groups with intra but not inter cross resistance developing, is well supported, though Hamon, J. (1953) *Bull. Soc. Path. exot.*, **46**, 454, claimed resistance developed to both groups when only one had been in use.

Finally there are the appendixes, dealing with formulæ devoted to the analysis of the factors affecting malarial transmission, and with those techniques most required by the malariologist. The former, in particular, will delight the heart of the mathematician while the whole subject is dealt with in an interesting, comprehensive and original manner. A most valuable addition to the bibliography of malaria.

**Memoirs of a Golden Age.** By Maurice Davidson. (Pp. xiii + 140; illustrated. 18s. 0d.) Oxford: Basil Blackwell. 1958.

This is a delightful collection of reminiscences, both grave and gay, of student-life at Oxford at the turn of the century, written by one who has a deep affection for his Alma Mater. The memories are not merely medical for we are given many vivid pen-pictures of learned classical scholars, musicians, and theologians, some of whom possessed odd quirks of character and habit, as, for example, the one who would only be measured for his trousers while seated on a chair.

The illustrations are a source of joy and by themselves would make it worth while to possess the book; we specially liked the sketch entitled "Responsions" in which the son addresses his father—"Hallo, father, I'm through, are you?" with the dolorous answer "No".

Every Oxford man and many who, like the reviewer, had not the privilege of being educated at that seat of learning, will enjoy this nostalgic "scrap-book".

The author thinks the spirit of the golden age has departed from Oxford. We are not convinced.

> 'Tis strange, in speaking of a golden age
> We always use the past and future tenses,
> And think how trivial the present stage
> Which crowds its imperfections on our senses;
> Yet may our children term the present date
> The Golden Age of Nineteen fifty-eight.

**Human Blood Coagulation and Its Disorders.** By Rosemary Biggs, B.Sc.(Lond.), Ph.D.(Toronto), M.D.(Lond.), and R. G. Macfarlane, M.A.(Oxon.), M.D.(Lond.), F.R.S. 2nd edit. (Pp. xxv + 476; illustrated; 42s.) Oxford: Blackwell Scientific Publications Ltd. 1957.

The appearance of a new edition within four years of the first is a consequence of the success of this book and also of the rapid advance in knowledge of blood coagulation and the hæmorrhagic disorders.

The authors were unfortunate in that the first edition was published almost simultaneously with two major events in the history of blood-coagulation research: the discovery of Christmas disease and the introduction of the thromboplastin-generation test. The present edition has been better timed; no comparable "break-throughs" in knowledge have taken place during its preparation and the authors have been able to complete their revision comparatively undisturbed by new discoveries. The result is a most readable and authoritative account of blood coagulation and its disorders.

All the new work receives critical mention. Christmas disease, PTA deficiency and von Willebrand's disease are surveyed in detail and an important section is devoted to the hypoprothrombinæmias and Factor-VII deficiency. There is a useful chapter on thrombosis and anticoagulant therapy. The technical section of the book has been expanded and a useful glossary of technical terms appended, in which synonyms for the various clotting factors may be found.

There is much to admire in this book and practically nothing to criticize. The reviewer would, however, like to suggest that some, at least, of the figures be redrawn when the next edition is prepared. Although they show what they are meant to, they are mostly not up to the standard of the rest of the book. Exception could also be taken to the size of the small print in the few places where it is used in the text, e.g. pp. 307–312. It is so small that a magnifying glass is almost a necessity.

# Section of Odontology

President—G. T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S., L.R.C.P.

[*October* 28, 1957]

## Some Observations on Costen's Mandibular Syndrome: Including a Review of 100 out of 500 Cases

### PRESIDENT'S ADDRESS

By GEORGE T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S., L.R.C.P.
*London*

#### INTRODUCTION

THE first part of this Address is a short commentary on Costen's syndrome; the second is a review of 100 treated cases of temporomandibular dysfunction out of more than 500. [A colour film of the treatment of a typical case was shown at the Meeting.] The subject matter is complementary to my two previous papers on this subject (Hankey, 1954, 1956) and should, if possible, be read in conjunction with them.

#### PART I.—A BRIEF DISCUSSION OF COSTEN'S SYNDROME

Costen, an American otolaryngologist, ascribed the following syndrome of symptoms to temporomandibular joint dysfunction: (1) Neuralgia of the second or third divisions of the V nerve. (2) Pain in and around the ears. (3) Stuffy sensation in the ears. (4) Pain up the back of the head and down the side of the neck. (5) Headaches, chiefly of the vertex. (6) Sinus pains. (7) Impaired hearing. (8) Tinnitus. (9) Altered sensations of the tongue and throat, including changes of taste.

In a series of papers between 1934 and 1956 Costen analysed a large number of cases and enunciated the hypothesis that the symptoms were due to one or more of the following: (1) Mandibular overclosure with distal condylar displacement and compression of the eustachian tube. (2) Actual direct erosion of the roof of the glenoid fossa and the tympanic plate. (3) Mesial pressure of the condyle on the chorda tympani. (4) Pressure of the retruded condyle on the auriculotemporal nerve.

Anatomically these explanations have not been substantiated (Zimmerman, 1951; Sicher, 1952; Shapiro and Truex, 1943).

Clinically erosion of the roof of the glenoid fossa is extremely rare—it has been found in none of my cases, and ear symptoms other than pain are almost completely absent.

Neuralgia of varying types and degree is the commonest and most distressing symptom, and can only be explained as being reflex in origin from the joint or masticatory muscles. Care must be taken to exclude other causes of pain, e.g. dental, sinus infection, &c. (Harris, 1937).

Although Costen has himself considerably modified his original views, and many of his concepts have since been found untenable, he has rendered a great service in pointing out the relationship between malocclusion, temporomandibular joint dysfunction and facial pain.

#### PART II.—AN ANALYSIS OF 100 TREATED CASES OF TEMPOROMANDIBULAR DYSFUNCTION

These cases comprise a chance collection of 100 out of more than 500 treated by myself privately or in my clinics at The London and St. Bartholomew's Hospitals in the course of the last ten years: 68 of them have been treated since my first analysis of 150 cases in 1953 (Hankey, 1954). This second analysis is put forward partly for comparison with the first but also as an attempt to answer some of the many questions put to me on this subject.

The statistics have been compiled from special Temporomandibular Clinic case-history sheets instituted by myself since 1953 and by means of questionnaire forms filled in at an actual re-examination of the patients in July 1957.

*Sex incidence.*—Table I reveals the same sex incidence as in most other publications on this subject, i.e. 4 females to 1 male. There is no specific reason why females should predominate to this extent.

*Age incidence.*—Table II shows that the 31–40 age-group is the largest and that 74% were aged between 20 and 50—the period when the permanent natural dentition is normally present.

*Symptoms both local and regional. 82 cases.*—Table III shows that 82 of the cases had local symptoms which could be related by the patient to the joint or to mandibular function. The symptoms were the same as previously described by myself (Hankey, 1954, 1955, 1956) and by many others, i.e. clicking with or without pain, occasional locking at first reducible but often eventually irreducible and merging into restricted opening, at first with pain and

TABLE I.—CASES EXAMINED AND SEX INCIDENCE

| | | |
|---|---|---|
| Males | 21 | |
| Females | 79 | [Females 4 to 1] |
| | 100 | |

TABLE II.—AGE INCIDENCE

| Years | Cases |
|---|---|
| 11–20 | 14 |
| 21–30 | 25 |
| 31–40 | 28 |
| 41–50 | 21 |
| Over 51 | 12 |
| | 100 |

TABLE III.—SYMPTOMS RELATED AND UNRELATED TO THE JOINT

| Symptoms | |
|---|---|
| Local. Related by patient to T.M. joint .. .. .. | 82 |
| Regional. Unrelated by patient to T.M. joint .. | 18 |
| | 100 |

spasm of muscles but later becoming painless after fibrous contractions or adhesions had taken place. Others complained of recurrent subluxation either primary or in the joint opposite to the restricted one. The type of pain complained of was spasmodic, short and sharp or else a dull continuous ache and the distribution was usually in the joint itself, up the auriculotemporal nerve, down the inferior dental nerve or along the side of the maxilla. Eating or movements of the mandible aggravated the pain. The fact that the joint or masticatory muscles were in some way involved was clearly indicated. The regional symptoms to be described were often superimposed. Patients in this group were often referred from an orthopædic surgeon.

*Symptoms—regional only.* 18 *cases.*—Table IV tabulates the symptoms of the 18

TABLE IV.—COMPLAINTS OF THE 18 CASES WITH REGIONAL BUT NO JOINT SYMPTOMS

| *Symptoms* | | |
|---|---|---|
| 1 | Neuralgia of 2nd or 3rd divisions of V nerve .. | 11 |
| 2 | Pain in and around ears .. .. .. .. | 10 |
| 3 | Headache, top of head .. .. .. .. | 6 |
| 4 | Pain up back of head or down side of neck .. | 5 |
| 5 | Painful spasm of muscles—2 masseter, 1 temporalis | 3 |
| 6 | Pain in throat or on swallowing .. .. .. | 1 |
| 7 | Tinnitus .. .. .. .. .. .. | 1 |
| 8 | Stuffy sensation in ears .. .. .. .. | — |
| 9 | Impaired hearing .. .. .. .. .. | — |
| 10 | Sinus pains .. .. .. .. .. .. | — |
| 11 | Altered taste or sensation of tongue .. .. | — |

NOTE: Many of the patients had a mixture of *symptoms* 1, 2, 3 and 4. *Symptoms* 8, 9, 10 and 11 are conspicuous by their absence.

patients who were unable to relate their complaints to the joint or to mandibular function. They consisted mainly of neuralgias of varying intensity and duration and not always limited to the distribution of the V nerve. The differential diagnosis was more difficult, but after eliminating all other possibilities, the source of the trouble was thought to be in the joint or its musculature. The symptoms described by Costen are included and it is at once apparent that deafness, giddiness, sinus pains and altered lingual sensation are all conspicuous by their absence, which conforms with my previous analysis; the only case with tinnitus also had earache—the pain was cured but not the tinnitus.

Most of this group of patients complained of *symptoms* 1 and 2: that is some form of neuralgia along the distribution of the second and third divisions of the V nerve or of pain in and around the ears. In the first place they often went to the neurologist or the otologist who were unable to account for the symptoms in their field. On examination, however, the pain described by the patient as being in the ear was, in fact, often found to be just anterior to the ear in the joint and on palpation the joint might be tender. This confusion is natural when it is remembered that the auriculotemporal nerve conveys sensation and pain from the anterior surface of the external auditory canal and from the anterior and upper part of the external surface of the tympanic membrane as well as from the joint and temporal region, the postero-inferior part of the external surface of the membrane being supplied by the vagus.

Headaches up the side and on the top of the head, *symptom* 3, were the next most frequent complaint: the area roughly corresponds to that supplied by the middle meningeal artery. A recurrent sensory nerve from the third division of the V nerve re-enters the skull through the foramen spinosum with this artery and supplies the dura mater in the same area of distribution. The pain can therefore be referred from other parts of the third division. So far the pain symptoms are in the area of the trigeminal and could all be due to stimulation of the auriculotemporal branch.

Pain up the back of the head and down the side of the neck and throat, *symptom* 4, is in the area supplied by the second and third cervical spinal nerves and is more difficult to explain in relation to the joint. The area of these nerves borders on and in some part overlaps the area of the trigeminal. Stimulation of II and III cervical can not only cause

pain in their sensory distribution but also, through their motor branches, can cause spasm and stiffness of the neck muscles and sternomastoid. The sensory root fibres of the trigeminal nerve concerned with pain, deep pressure and temperature pass down through the pons and medulla as low as the second cervical segment (Harris, 1937). By synaptic overflow therefore the cervical nerves can be stimulated and give rise to referred pain, the point of origin being in the area of the trigeminal. It has also been noted that infected antra may be the remote cause of spasm and pain of the muscles up the back of the neck.

Muscles in spasm or partial spasm, *symptom* 5, become painful of themselves although inflammation or trauma may have been the original cause of the spasm. If the meniscus or part of the synovial membrane of the temporomandibular joint is accidentally nipped, there is immediate pain; inflammatory reaction and effusion will be followed by some degree of protective muscular spasm to restrict movement and avoid further pain during the period of healing. If the trauma to the joint is chronic the muscular reaction will be the same. Similarly, if the occlusion is at fault and undue or unequal stresses are thrown on certain teeth and their supporting structures then, as pointed out by Ballard (1956) and others, either the teeth are gradually forced into a more comfortable position or they become painful and loose and have to be extracted or, by the agency of the acutely developed proprioceptive senses conveyed in the nerves of the periodontal and supporting tissues, the mandible as a whole by reflex muscular action moves distally, mesially or eccentrically into a bite of accommodation thereby avoiding the painful stimulus. This unnatural movement upsets the normal delicate balance between the muscles on either side of the mandible and may result in muscle spasm and pain without evidence that the joints are also involved. There is a great field here for further electromyographic study. Schwartz and Cobin (1957) are of the opinion that painful spasm of the masticatory muscles is the commonest symptom associated with temporomandibular dysfunction, malocclusion being only a contributory factor.

Pain in the throat or on swallowing, *symptom* 6, may well have a similar muscular explanation for its cause. If the muscles of the neck or mandible or both can be put into a state of tension or spasm through inco-ordinated or unusual movements, then the normally smooth process of swallowing can likewise be disturbed.

Transitory tinnitus and deafness, *symptoms* 7, 8, 9, can be brought on by trauma or infection of the internal pterygoid muscle by spread from an infected wisdom tooth or following an inferior dental nerve block anæsthesia, the reason being that the motor nerve to the tensor tympani and tensor palati muscles comes off the nerve to the internal pterygoid which may be involved. The sensory nerve of the inner surface of the tympanic membrane and the lining of the eustachian tube is a branch of the glossopharyngeal; catarrhal or other blockage of the eustachian tube can cause deafness or deep ear pain but it is impossible for the retruded condyle to effect this by direct pressure.

Sinus pains, *symptom* 10, can be referred to the area of the joint and the reverse is possible, both being within the distribution of the same nerve.

And lastly, altered sensation or pain in the anterior part of the tongue, *symptom* 11, could be referred for the same reason from the joint along the lingual nerve. But the chorda tympani nerve, a branch of VII, has no pain fibres, is concerned with taste only and has no relation close enough to the joint to become involved. Although none of these 100 patients happens to have complained of lingual symptoms, there have been several among the other 400.

One in particular, an edentulous woman aged 70, had been unable to wear her lower full denture for a long time owing to extreme sensitivity and pain of the right anterior two-thirds of the tongue; she had recently only been able to eat the softest of food with great difficulty and was losing weight. The tongue was so tender that she could not tolerate the taking of a lower impression until a right inferior dental and lingual nerve block had been given. She had marked overclosure with condylar retrusion. The lower denture was raised to the correct height with an overlay and before insertion in the mouth a right lingual nerve block with proctocaine was given which lasted for ten days. She was then able to wear the denture which gave support to her mandible and prevented overclosure. At the end of ten days one more lingual Proctocaine injection was given. From then onwards the pain in the tongue disappeared and she was able to eat in comfort.

*Details of the 18 cases with regional symptoms only.*—A higher proportion than usual were male, 11 were over 40 years of age and only 1 under 30. 7 cases were edentulous and all these were overclosed with an increased free-way space, consequent on alveolar absorption with loss of vertical dimension over a period of years or due to full dentures set up at the wrong height *ab initio*. It is interesting to note that only 4 of these 7 edentulous cases showed condylar retrusion on X-ray with the teeth in occlusion: the other 3 had normally placed condyles so that their pain was probably of muscular origin. Among the remainder, loss of molar support was the common occlusal deformity.

X-rays of the joints showed that 9 of the 18 cases, including the 4 edentulous ones, had retruded condyles with the teeth in occlusion; the remainder were normally placed. In

cases where the condyles have been retruded it is usual to believe that the backward pressure on the posterior part of the joint and on the posterior bilaminar attachments of the meniscus where the nerve filaments and vessels supplying the joint are mostly situated, is the origin of the pain; but where the condyles are not so displaced, the pain may well originate in the muscles which are constantly contracting to prevent a displacement which would otherwise occur as a result of malocclusion. Prosthetic bite rehabilitation was provided for all 18 cases by overlaid appliances or by partial or full dentures. All of these 18 cases were eventually much better as the result of treatment and eleven of them were completely cured. None of them was psychopathic.

*Angle's classification and edentulous cases.*—Table V is self-explanatory. More than half the cases had occlusions which could be classified as Angle's Class I; in 6 of these, initially edge to edge, the mandibular incisors had subsided into a labial relation to the uppers owing to lack of molar support and consequent overclosure. Only 27 were Class II: not as many as has previously been supposed.

TABLE V.—ANGLE'S CLASSIFICATION AND EDENTULOUS CASES

| | |
|---|---|
| Angle's Class I .. .. .. | 57 |
| ,, ,, II, Div. 1 .. .. | 16 |
| ,, ,, II, Div. 2 .. .. | 11 |
| ,, ,, III .. .. .. | 2 |
| Edentulous .. .. .. .. | 14 |
| | 100 |

NOTE: 6 cases originally edge-to-edge Class I had lapsed into pseudo-Class III due to loss of molar support.

TABLE VI.—MALOCCLUSIONS

| | | |
|---|---|---|
| Overclosure: | | |
| Edentulous .. .. | 14 | |
| Loss of molar support .. | 8 | |
| Mutilations .. .. | 2 | |
| Angle's Class II, Div. 2 .. | 4 | |
| | — | 28 |
| Mutilations .. .. .. .. | | 24 |
| Loss of molar support .. .. .. | | 22 |
| Cuspal deflection .. .. .. | | 17 |
| Cross bite .. .. .. .. | | 6 |
| Normal .. .. .. .. .. | | 3 |
| | | 100 |

NOTE: The total number of cases with loss of molar support = 30. 50% of the cases of overclosure were edentulous in one or both jaws. A large number of the cases were also locked against lateral grinding.

*Malocclusions.*—Table VI shows a simplified grouping of the types of malocclusion encountered. 28 were overclosed, of whom half were edentulous; all the edentulous cases were overclosed; 22 had loss of molar support, increased to 30 if 8 overclosed cases are added. Mutilations (haphazard extractions which allow drifting, tilting and over-eruption of the teeth remaining) accounted for 24 cases. Irregularities and cuspal interference 17, cross bites 6, made up the rest. Only 3 could be considered completely normal. It would be interesting to survey a large number of patients to see how many are normal in a civilized community.

*Joint X-ray findings.*—Table VII is shown in order to answer queries as to whether T.M.

TABLE VII.—JOINT X-RAY FINDINGS

| | | | | |
|---|---|---|---|---|
| Normal .. .. .. .. .. .. .. .. | | | | 34 |
| Condylar retrusion, with the teeth in functional occlusion: | | | | |
| One side only | 16 | Both sides | 15 | 31 |
| Condylar subluxation, mouth wide open: | | | | |
| One side only | 5 | Both sides | 2 | 7 |
| Condylar restriction of forward translation: | | | | |
| One side only | 18 | Both sides | 2 | 20 |
| Pathological changes in outline: | | | | |
| Osteochondritis | 1 | Rheumatoid arthritis | 2 | |
| Osteoarthritis | 1 | Neisserian infection | 1 | |
| Malformation of condyles | 3 | | | 8 |
| | | | | 100 |

joint X-rays are of value, and if they are, what conclusions can be drawn from them. J. R. Thompson in many writings (1946, 1949, 1951) has emphasized the importance of the rest position of the condyles in the glenoid fossæ, particularly in relation to the correction of occlusal deformities, and largely due to his influence it came to be accepted that a pure hinge movement took place in the lower compartment of the joint during closure of the mandible from rest to occlusion and without further translation backwards or upwards of the condyles. Recently, however, Nevakari (1956) has denied this supposition and states that in this same final path of closure the condyle in all cases undergoes a slight translatory movement upwards and backwards averaging 1 mm.—which is very little and difficult, if not impossible, to demonstrate on an ordinary X-ray. A translation during closure from

rest, of more than 2 mm., could therefore still be accepted as abnormal. Husted (1956) is very sceptical about the usefulness of X-ray films to determine the influence of bite displacements on the position of the condyle in the glenoid fossa. There is no doubt that, unless a special detailed technique is employed either by the dental specialist himself, or by the radiographer in the closest association and full understanding of the requirements, many routine X-rays of the joint are valueless, if not misleading. The only variants permissible are the controlled jaw movements; the relative position of the head, film and tube must be static and possible to repeat in an identical manner at the same or a later sitting. (A satisfactory technique for taking transcranial lateral oblique films of the T.M. joint was shown later.) No two patients have condyles or fossæ the same shape or size; often the two sides vary in the same individual, Very rarely will a gross pathology be revealed in these cases of dysfunction or pain; the search is for abnormal movement or displacement.

In this series 34 cases had normal X-ray films. 31 cases showed condylar retrusion with the teeth in occlusion as compared with the resting position; 16 of these were retruded on one side only suggesting a lateral displacement of the mandible by cuspal interference as opposed to centric closure. 15 were retruded on both sides suggesting a displacement backwards of the mandible as a whole. 7 cases showed condylar subluxation when the mouth was wide open, often in Angle's Class III or pseudo Class III occlusions, sometimes on one side only when the other was restricted. 20 cases showed limited forward movement of the condyles on opening, suggesting meniscal block or muscle spasm or both. Only 8 cases showed pathological change of joint outline—1 due to osteoarthritis, 2 to generalized rheumatoid arthritis, 1 to Neisserian infection, 1 to osteochondritis of the condyle, and 3 to congenitally malformed condyles.

*Psychiatric assessment.*—Table VIII is an effort to answer the suggestion frequently

TABLE VIII.—PSYCHIATRIC ASSESSMENT

| | Sex | Age group | Result | |
|---|---|---|---|---|
| Psycho-neurotic | F | 20 | Cure | |
| | F | 20 | Cure | |
| | M | 40 | Unchanged | |
| | | | | 3 |
| Anxiety neurosis | F | 50 | Better | |
| | F | 40 | Cure | |
| | F | 30 | Cure | |
| | F | 30 | Cure | |
| | F | 20 | Better | |
| | F | 10 | Better | |
| | M | 30 | Cure | |
| | M | 30 | Better | |
| | M | 30 | Unchanged | |
| | | | | 9 |
| | | | | 12 |

*Summary*:

Average age over 30 excepting 4 females:

| | |
|---|---|
| 5 females, 1 male—cured .. .. | 6 |
| 3 females, 1 male—better .. .. | 4 |
| 2 males—unchanged .. | 2 |
| 8 4 | 12 |

Psychological reaction of remainder was average for patients attending a hospital for medical treatment.

made that a large proportion of the patients complaining of mandibular syndrome symptoms are neurotic. Out of these 100 patients only 3 were definitely diagnosed as psychoneurotic; 9 more suffered from a lesser degree of anxiety neurosis, and there were a few more women who manifested menopausal instability. It is interesting to note that 4 of these 12 cases were male and that the only 2 cases not improved by treatment were also male. Of the 12, 6 were cured of their mandibular syndrome, 4 were much improved, 2 were no better. The average age of these patients was 30 years or more except for 4 young females. By and large it seemed that the psychological reaction of the rest of these 100 patients was average and what is to be expected of a patient attending a large hospital for medical treatment.

Staton (1955) reviewed a group of patients suffering from mandibular syndrome symptoms from the psychosomatic aspect. He considers that a mild neurosis occurs in all types of patients attending for medical treatment, but that the syndrome may occur coincidentally without relation to neurosis. He accepts the possibility of a psychosomatic precipitation factor in the initiation of pain episodes and that the onset of symptoms may coincide with emotional stress, anxiety or tension state and may terminate with it, but that this should not deviate attention from applying accepted and established therapy. With the physical correction of anatomical derangement, the psychosomatic precipitation of painful episodes should become impossible.

*Treatment.*—Table IX shows the relative frequency of employment of the various lines of treatment of these cases. Almost 80% were supplied with some form of removable prosthetic appliance because it was impossible to take the strain off the joints, relieve muscle spasm and provide a reasonable, balanced occlusion in a centric relation by other means. It is, of course, possible to rehabilitate some occlusions by means of fixed onlays

TABLE IX.—TREATMENT

| | | | |
|---|---|---|---|
| Voluntary muscle control and exercises | 17 | Training flange | 2 |
| Physiotherapy | 31 | Orthodontia | 6 |
| Immobilization | 7 | Extractions—8 for wisdoms | 20 |
| Selective cuspal grinding | 17 | Meniscectomy | 5 |
| Joint injections—8 hydrocortisone 2 sclerosant | 10 | Prosthetic appliances | 79 |

NOTE.—Two or more lines of treatment were often used on the same patient, but the figures show the percentage frequency of employment of each kind.

and bridges, but this type of work is terribly time-consuming, extremely expensive and involves the highest technical skill only possessed by specialists in crown and bridge work. It is therefore only available for the few, and impracticable in a State medical service, not to mention the fact that nothing is worse for a painful joint accompanied by muscle spasm than long hours in the chair with the mouth open especially when it is remembered that very often the commencement of joint symptoms dates from just such a session. Moreover in several instances the mandibular syndrome has been the direct result of crown and bridge work which, far from rehabilitating the bite, has produced unnatural strains and stresses and thrown the occlusion off centric. A removable plastic overlaid appliance is easily and cheaply made with the minimum of inconvenience to the patient and supplies an immediate remedy for the pain; later, when the spasm and pain have been relieved, it can sometimes be worn less and less, perhaps only at night, or eventually discarded altogether. Others who have many teeth missing, have to wear a permanent appliance which serves both as an overlay and as a denture.

Among the 21 patients who were not treated with prosthetic appliances were those with only minor degrees of malocclusion which could be cured by selective grinding, muscle exercises and self-control. It is also clear from the figures that many patients required several lines of treatment.

Injections into the periarticular tissues and joint cavities of hydrocortisone have proved of great benefit in cases whose pain was not relieved by bite rehabilitation alone or in whom there was an established mild degree of osteoarthritis. Strean (1957) has recently published an excellent monograph on the uses of cortisone in dentistry. Pinkey (1955) reports the effect of hydrocortisone on some 350 patients suffering from mandibular syndrome. Its use is empirical, non-specific and purely palliative; its real action is unknown, but it relieves pain and probably aids in the healing of injured tissues. It should be used only as an adjunct to basic dental treatment. The actual intra-articular injection of 1 c.c. of hydrocortisone using a 2 c.c. glass record syringe with a 22 gauge needle, is quite simple and painless if preceded by a superficial and periarticular injection of about 1 c.c. of 2% Xylocaine, using a fine needle. The joint is most easily entered from behind when the mouth is half-open and the condyle is drawn forwards. The point of entry, by palpation, is about $\frac{1}{2}$ in. anterior to the tragus of the ear. Loose, recurrently subluxating joints can be injected in the same way with a mild sclerosant such as sodium psylliate or a 2% phenol in glycerin and glucose, in order to cause a contraction of the capsule. Endografen is an excellent contrast agent for arthrography, gives no painful reaction and is rapidly absorbed. The only disturbing feature for the patient of these injections is an occasional but purely temporary facial palsy brought on by the Xylocaine; the patient should be warned of the possibility beforehand.

Unilateral meniscectomy was performed on 5 cases out of the 100, and all of these were among my early cases treated prior to 1953. Operation was only recommended after all conservative treatment had failed and where there was an obvious meniscal displacement or obstruction with continued pain. In all cases the operation cured the pain but forward condylar translation afterwards tended to be restricted owing to capsular contraction. Sometimes the originally unaffected joint then became overmobile by way of compensation for the limited movement of the operated side and later tended to give trouble. It would seem that balanced and equal muscular action on both sides is of great importance and it is debatable whether the meniscectomy should not be bilateral. The patient only needs to be in hospital about a week for meniscectomy and there is no visible post-operative scar. Exercises or even a training flange should be instituted as soon afterwards as possible in order to obtain the maximum condylar movement. Rehabilitation of the bite is still essential after the operation. In my first 150 cases, 16% underwent surgery (Hankey, 1954), in the next 260 only 3% (Hankey, 1956), and since then an even smaller percentage.

The rationale of bite rehabilitation in the treatment of temporomandibular dysfunction has been dealt with in detail in my previous papers to which reference has already been made. In brief, however, the aim in all cases of mandibular syndrome attributable to malocclusion is to restore that occlusion to the normal centric level and to maintain it in equilibrium so that the teeth can grind freely in all directions without locking, bumping or unequal muscular strains and so that the condyles at the same time are symmetrically

placed and correspond as closely as possible to their resting positions when the teeth or appliances come together in function.

TABLE X.—PROSTHETIC DETAILS

| | |
|---|---|
| Trial acrylic overlays: upper 4, lower 28 | 32 |
| Permanent chrome-cobalt overlays (after trial acrylic): upper 4, lower 14 | 18 |
| Permanent full dentures | 14 |
| Permanent partial dentures | 9 |
| Orthodontic appliances | 6 |
| No prosthetic treatment | 15 |
| Did not return after 1 visit | 6 |
| | 100 |

NOTE: The final permanent overlay figure will probably lie between 20% and 25%. The overlays and full dentures increased the vertical dimension, and provided a balanced occlusion which could grind freely in all directions, and permit the mandible to find its natural centric relation.

*Prosthetic details.*—Table X shows the types of appliances made for those 79 in Table IX who needed prosthetic aids and at the same time it demonstrates the percentage of cases who needed permanent appliances. 50 cases were fitted with acrylic overlays and of these 18 were later fitted with permanent chrome-cobalt skeleton type overlays; a time-consuming, highly skilled mechanical project. It is likely that the final permanent overlay figure will be as high as 25; the output of the laboratory is a limiting factor. Patients for permanent appliances are taken in rotation; in the meantime new cases in pain have to be dealt with by priority and supplied with trial acrylic appliances. This means that the trial appliances have to be worn a long time. On average they are very comfortable if streamlined and made as small as possible consistent with strength, and with the maximum tongue room.

The 14 overclosed edentulous cases all required permanent full dentures raised to the correct vertical dimension. In the first instance it is often a good plan to fix a trial acrylic overlay to the old lower in order to find the correct and most comfortable occlusion; the new denture is later made to this height and bite.

The overlays and full dentures, all increasing the vertical dimension, together totalled 64% and of these, 32 were permanent and 9 more cases required partial tooth-borne dentures without opening the bite. 6 under 20 years of age were treated orthodontically. 15 cases did not require prosthetic appliances, but every case necessitated the taking of impressions, face-bow readings and the mounting of the models on the dentatus articulator. 6 cases did not return for further treatment after the first visit, but all returned for examination or answered the questionnaire in July 1957.

*Attendances for treatment.*—Table XI gives an idea of the average number of attendances

TABLE XI.—AVERAGE NUMBER OF ATTENDANCES FOR TREATMENT

| | |
|---|---|
| Initial examination, investigation and first appliance | 5 visits spread over two months |
| Follow-up, for adjustment, &c. | 3 visits spread over next four months |
| Permanent appliance (after six months' interval or more) | 4 visits spread over one month |
| Averaging | 12 visits spread over twelve months |

Physiotherapy, short wave diathermy, involved additional attendances, e.g. 3 visits per week for four weeks.

of each patient necessary for prosthetic treatment and the amount of time involved. In addition there must be reckoned the mechanic's time spent in the laboratory in the making of the appliances and any additional attendances necessary for physiotherapy, &c.

On average 5 visits spread over two months from initial examination to fitting of trial appliance were necessary per patient; 3 more visits spread over the next four months for adjustment and follow-up were often needed. If a permanent appliance was essential later, 4 more visits were entailed. Such a patient would have to attend at least 12 times in the course of a year.

It can therefore be readily understood that the work of a temporomandibular clinic rapidly accumulates and that it requires the services of a highly trained staff to deal with it efficiently.

*Caries incidence under 50 overlays in Table X.*—Table XII shows that 5 of the 50 cases wearing movable overlaid appliances developed superficial enamel caries of the teeth beneath them apparently in spite of reasonable oral hygiene, but probably the hygiene was not as good as stated; with improved instruction and care it should be possible to lower this figure. The remainder did not seem to be more prone to caries than the average.

*Results of treatment.*—Table XIII shows that, following treatment, 60 of the 100 cases were completely cured and another 34 were much improved but not entirely free from symptoms. The time factor for improvement or cure is also shown; 51% were cured within

TABLE XII.—CARIES UNDER 50 OVERLAYS

| | |
|---|---|
| In spite of reasonable care—5 cases = 10% | |
| Remainder | —normal incidence |

TABLE XIII.—RESULTS OF TREATMENT

| | | | | |
|---|---|---|---|---|
| Improved | 4 months | .. .. | 23 | |
| | 12 ,, | .. .. | 8 | 34 |
| | 24 ,, | .. .. | 3 | |
| Cured | 2 ,, | .. .. | 27 | |
| | 7 ,, | .. .. | 24 | |
| | 18 ,, | .. .. | 7 | 60 |
| | 24 ,, | .. .. | 2 | |
| Unchanged | .. .. | .. .. | 6 | |
| | | | 100 | |

seven months; another 31% were much better within twelve months, the remainder took anything up to two years. Only 6 cases remained much the same and failed to respond to treatment. An assessment and analysis of the failures must be made in the future. The percentage of absolute cures is not as high as in my previous analysis, but perhaps this can be partly explained by the fact that as time goes on a higher percentage of difficult cases are referred to my clinics for treatment while the less difficult ones are dealt with locally.

A colour film, with sound commentary, was then shown. The film demonstrated the examination, investigation and treatment of a typical case of temporomandibular dysfunction.

SUMMARY

The ear symptoms described by Costen in his mandibular syndrome, except for pain, are almost non-existent: but the neuralgias are very real.

Distressing facial, head and neck neuralgias without joint symptoms but due to mandibular displacement or muscular tension, were present in 18 out of 100 cases; these 100 cases are reviewed.

An explanation for the wide area covered by the neuralgias is given.

34% of the T.M. joint X-rays appeared normal, 58% showed abnormal condylar movement, 8% showed pathological change.

3% of the patients were definitely psychoneurotic: another 9% suffered from a mild anxiety state.

97% had some form of malocclusion.

79% required prosthetic appliances. 8% were helped by intracapsular injections of hydrocortisone: 5% required meniscectomy.

20% required permanent overlaid appliances: another 30% required trial overlays.

A 10% increase of caries incidence beneath the 50 overlays was found (5% of the total).

60% were cured, 34% much improved, 6% unchanged.

Average number of attendances for conservative treatment was 8, spread over six months.

*Acknowledgments.*—My grateful thanks are due to my many professional colleagues for their co-operation in the collection of the material for this paper, but especially to Mr. J. L. Marsden, senior registrar, and Mr. W. E. Berwick, registrar, for their help in the re-examination of the cases and in the staging of the film.

For the making of the film I am indebted to Mr. M. K. Harrison, medical photographer, who did all the photography, to Mr. Love, senior radiographer, for the section on radiography of the T.M. joint, to Mr. J. Elliot, senior surgical technician, for demonstrating the laboratory techniques, and to the various other members of the staff of the Dental Department, St. Bartholomew's Hospital, for their enthusiastic support.

## REFERENCES

BALLARD, C. F. (1956) *Proc. R. Soc. Med.*, **49,** 994.
COSTEN, J. B. (1934) *Ann. Otol. Rhin., Laryng.*, **43,** 1.
—— (1936) *J. Amer. med. Ass.*, **107,** 252.
—— (1944) *Ann. Otol. Rhin., Laryng.*, **53,** 655.
—— (1956) *Ann. Otol. Rhin., Laryng.*, **65,** 35.
HANKEY, G. T. (1954) *Brit. dent. J.*, **97,** 249.
—— (1955) *Lond. Hosp. Gaz.*, **58,** No. 3. Clinical Supplement.
—— (1956) *Proc. R. Soc. Med.*, **49,** 983.
HARRIS, W. (1937) The Facial Neuralgias. Oxford.
HUSTED, E. (1956) *Acta odont. scand.*, **14,** 119.
NEVAKARI, K. (1956) *Acta odont. scand.*, **14,** Suppl. 19.
PINKEY, W. P. (1955) *Arch. Otolaryng., Chicago*, **61,** 594.
SARNAT, B. G., ed. (1951) The Temporomandibular Joint. Springfield, Ill.
SCHWARTZ, L. L., and COBIN, H. P. (1957) *Oral Surg.*, **10,** 339.
SHAPIRO, H. H., and TRUEX, R. C. (1943) *J. Amer. dent. Ass.*, **30,** 1147.
SICHER, H. (1952) Oral Anatomy. London.
STATON, Y. A. (1955) *Arch. Otolaryng., Chicago*, **62,** 370.
STREAN, L. P. (1957) Cortisone in Dentistry. London.
THOMPSON, J. R. (1946) *J. Amer. dent. Ass.*, **33,** 162.
—— (1949) *Angle Orthodont.*, **19,** 162.
—— (1951) In: Sarnat (1951).
ZIMMERMAN, A. A. (1951) In: Sarnat (1951).



## Front-line weapon

Since its introduction, 'Ilotycin' brand erythromycin has established itself as a safe and potent oral antibiotic. Clinical experience has shown that it can play a vital part as a front-line weapon against a wide range of infections. 'Ilotycin' has a penicillin-like antibacterial spectrum, is powerfully bactericidal, has negligible effect on the normal intestinal flora, and is fully effective by mouth. It has accordingly become the logical first choice after penicillin in the treatment of common infections.

Recent reports have stressed the value of 'Ilotycin' in treating the serious complications of influenza.

The average daily dose is 1 Gm., increased in severe infections.

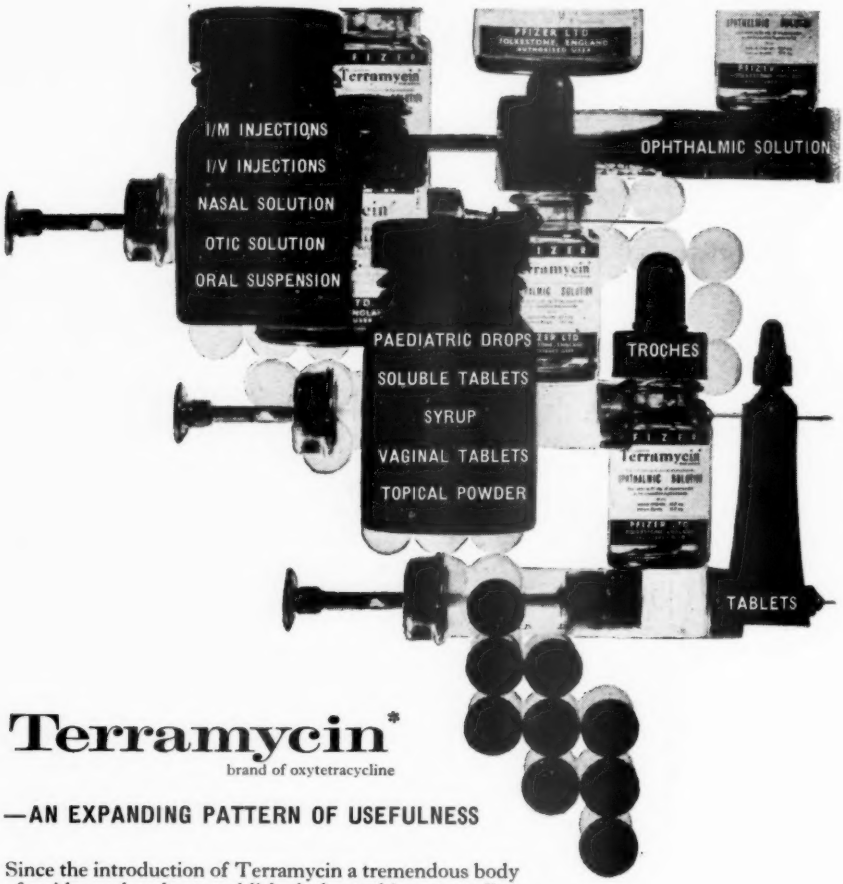
'Ilotycin' is available as Tablets of 100 mg. and 250 mg.; also as 'Ilotycin' Paediatric and as 'Ilotycin Glucoheptonate' Intravenous.

**'ILOTYCIN'**

THE ORIGINAL ERYTHROMYCIN

DISCOVERED BY *Lilly*

**ELI LILLY & COMPANY LIMITED**
**BASINGSTOKE ENGLAND**




# Terramycin*

brand of oxytetracycline

## —AN EXPANDING PATTERN OF USEFULNESS

Since the introduction of Terramycin a tremendous body of evidence has been published about this outstanding broad-spectrum antibiotic. Today, its value is known and established in almost every type of disease where infection is a factor. Following the course of this development we have introduced a wide variety of dosage forms, so that the clinical effectiveness of Terramycin should be enhanced by convenience and acceptability of presentation.

The very bulk of the available evidence becomes almost an embarrassment to the busy practitioner who — having accepted the clinical value of Terramycin — wants a concise picture of indications, dosage, therapeutic effect and possible side effects, in some specific condition. To overcome this problem we are preparing a series of brief monographs on the use of Terramycin in specific groups of indications. The second of these, 'Terramycin in the treatment of Genito-Urinary Infections,' is now available.

**WHERE A BROAD-SPECTRUM ANTIBIOTIC IS INDICATED**

**Terramycin**

**PROVED CLINICAL EFFECTIVENESS**
**WIDE MARGIN OF SAFETY**
**COMPLETE RANGE OF DOSAGE FORMS**

**PFIZER PHARMACEUTICALS**
*Manufactured at Sandwich and processed at Folkestone, Kent*

Pfizer

*Registered Trade Mark

067/P

# Section of Orthopædics

President—J. A. CHOLMELEY, F.R.C.S.

[*October* 1, 1957]

THE following cases were shown:

**Early Painful Osteoarthritis of the Hip-joint.**—Mr. K. I. NISSEN.

A woman aged 50. Six months ago the vertical system of medullary blood vessels was interrupted at the intertrochanteric level by transverse forage through a small hole in the lateral cortex. The pain was relieved immediately. It is suggested that the mechanism of relief of pain is a reduction in the level of hyperæmia of the head and neck of the femur, similar to the effect produced by a McMurray osteotomy.

**Three Cases of Fractured Scaphoid, Treated by Internal Fixation with Lag Screw.**—Mr. ROY MAUDSLEY.

**Craniopharyngioma and Slipped Upper Femoral Epiphysis.**—Mr. B. J. S. GROGONO.

Female aged 18 showing signs of immaturity and retarded growth. Craniopharyngioma first diagnosed at 12 years, subsequently controlled by aspiration, partial excision and Torkilsden's short-circuiting operation for internal hydrocephalus.

Complications: Homonymous hemianopia and diabetes insipidus (controlled by pituitary snuff). Slipped left femoral epiphysis not affected by traction but fusing soundly in slipped position while opposite femoral epiphysis remains unfused.

Residual deformity of left hip but no pain.

**Four Cases of Amputation of the Fifth Ray in the Foot.**—Mr. B. J. S. GROGONO.

**Albers-Schönberg Disease Followed Since Childhood with Multiple Fractures.**—Mr. W. D. GRAHAM (for Mr. P. H. NEWMAN).

**Spontaneous Rupture of Extensor Tendon to Right Ring Finger.**—Mr. E. H. HAMBLY.

**Oblique Compound Fracture of Tibia, Treated by External Fixation with a Compression Calliper.**—Mr. W. H. GERVIS.

**Two Cases of Arthrodesis of the Hip-joint by a Modified Ilio-femoral Graft.**—Mr. A. C. BINGOLD.

**(1) Solitary Eosinophilic Granuloma of Right Ilium. (2) Solitary Xanthoma of Left Acromion.**—Mr. B. LAWSON.

**Congenital Contracture of Left Hand (? Pseudo-Dupuytren).**—Mr. B. LAWSON.

Female aged 18 months. First seen at age of 7 weeks with severe flexion contracture of middle finger and slighter of ring finger; palmar fascia adherent to thickened palmar skin with a thickened band across anterior aspect of 3rd metacarpophalangeal joint, fixed ulnar deviation of wrist. Daily stretchings, followed by "lively wire" splint. Child now also presents thickening of subcutaneous tissue of forearm extending up postero-lateral aspect of arm nearly to shoulder, and limitation of wrist and elbow movements.

**Alkaptonuria (Ochronosis).**—Mr. P. I. BUSFIELD (for Mr. G. P. ARDEN).

[*November* 5, 1957]

# Tendon Transplants in Poliomyelitis and in Obstetrical Palsy
## [*Summary*]

By JOSEPH BARR, M.D.
*Boston, Mass., U.S.A.*

**Dr. Joseph Barr,** in discussing certain aspects of tendon transplantations for anterior poliomyelitis, said that in his belief such transplantations should rarely be done earlier than sixteen to twenty-four months after the attack; by that time the patient had reached a stage of functional stability and a proper assessment of the best available surgical procedure could be made. While an accurate muscle chart was useful, he had never found this in itself sufficient evidence on which to assess the need for any particular operation. The vital factor was the functional examination and this might have to be repeated several times before all relevant factors could be evaluated. This gave time both for the surgeon and the patient to decide which was the most significant functional disability, the relief of which would be most valuable to the patient. Deformities once started tended to increase steadily throughout growth. It was important not to do tendon transplants too early because, for example, a foot which by tendon transplantation had been correctly balanced in early life might very well become unbalanced as the result of later growth. An exception to this rule was calcaneo-valgus deformity, for which early intervention was indicated and where he felt that there was still a place in a few cases for tenodesis of the tendo achillis. It was true that there was a risk of later equinus, developing as a result of this tenodesis, but the final state, as far as securing a balanced foot was concerned, was better. In the lower limb he thought there was a considerable risk of "over-bracing", certainly in the United States and very probably in other countries too. This led to disuse of the remaining muscles and was positively harmful at times.

The prerequisites of successful tendon transplantation were now well established. There must be no deformity present, or any such deformity must be corrected before operation. The transplant must carry sufficient power, the line of pull must be as direct as possible; he preferred to anchor his tendon to bone if possible. It was, of course, vital to preserve the blood and nerve supply, and as far as the question of tension was concerned, this was a matter of experience, but there should be "just enough" tension in the tendon when the joint was in the over-corrected position. Although long immobilization was not necessarily indicated, protection of the transplanted tendon must continue for a long time. He also stressed the need for expert physiotherapy and re-education if the best results were to be obtained.

He then turned to certain specific problems. Starting with the hand, for opponens paralysis he recommended the transplant of the flexor digitorum sublimis tendon of the ring finger, and said he had found it unnecessary to pass it round the tendon of flexor carpi ulnaris as a pulley; it could be freed in the palmar space and from there taken directly to metacarpophalangeal joint of the thumb. The tendon should be freed from the ring finger almost at its insertion; if a long stump were left it could become adherent and cause flexion deformity of the proximal interphalangeal joint. Even so he recommended the use of a splint to keep this finger in extension for a week or so after operation. The two slips of tendon thus obtained were sutured one to the phalanx and one to the metacarpal head; in cases where there was paralysis of the extensors of the thumb, it was important that one slip should be inserted into the extensor tendon to regain this movement.

He discussed the standard transplant of the wrist flexors into the finger and thumb extensors, recommending that palmaris longus should be passed to the thumb abductor and short extensor and both flexor carpi radialis and flexor carpi ulnaris into the long thumb extensor and the common finger extensors. The pronator teres should be inserted into the radial wrist extensors. Arthrodesis of the wrist was not popular with patients and should be strictly reserved for those cases where insufficient transplants were available. It should be done *after* any possible transplant operations.

To provide flexion at the elbow he considered the Steindler operation a good one, but recommended that the deep layer of the common flexor origin should be left intact and only the superficial layer transplanted proximally. The common extensor origin could also be transplanted proximally up the humerus if necessary, but this was a more difficult procedure.

To provide abduction of the shoulder he was willing to use any and all muscles available and had sometimes used trapezius, coracobrachialis and the short head of biceps, and the

long head of triceps all in one case. Turning for a moment to obstetrical paralyses, he recommended that for Erb's palsy a transplant posteriorly of the subscapularis tendon into that of teres minor was very helpful in providing external rotation, so that when the arm was abducted the hand could then be brought to the mouth. He considered this a better procedure than the standard Sever procedure or a humeral osteotomy.

In paralyses involving the trunk early recognition of scoliosis and adequate protection was essential; progressive cases should not be left too late but should be treated by correction and spinal fusion over a great length of the spine.

In discussing paralyses around the foot and ankle he considered that an ankle fusion alone was in many cases a most useful operation and in young children was a better procedure than the pan-arthrodesis, at least as a primary operation. A central graft passed through the middle of the lower tibial epiphysis into the body of the talus would promote fusion without interfering with the growth of the tibial epiphysis. When the peronei were going to be used as transplants into the dorsum of the foot, it was important that the peroneus brevis alone should be used if a functioning tibialis anterior was present to avoid the cocking-up of the metatarsophalangeal joint of the big toe, and if tibialis anterior were absent then peroneus longus should be used to avoid the formation of callosities under the first metatarsal head. If the tibialis posterior were going to be used, he recommended that a window should be cut out of the interosseous membrane before the tendon was passed forward to give it free passage and movement in this region; its function might be limited if it were simply pushed through a hole forced in the membrane.

In the case of quadriceps insufficiency, biceps and semitendinosus alone should be used in order to avoid the development of a back knee. Furthermore the biceps tendon should be transplanted into the patella along the medial side of the femur, which provided a more direct route and did away with the danger of lateral subluxation of the patella which not infrequently resulted from transplants of this tendon done on the outer side of the thigh. He mentioned that a flexion-abduction contracture of the hip was not due to *contracture* in the ilio-tibial tract, which from its very structure was not capable of contracting. The point was that longitudinal growth of the ilio-tibial tract did not keep pace with the growth of the bone. He had found the erector spinæ transplant a very satisfactory one in suitably selected cases.

In cases of unequal leg length in adults he had abandoned leg-lengthening as it carried too many risks, and he recommended shortening of the longer limb. Leg shortening from poliomyelitis was not a significant problem in patients who had suffered the disease after the age of 11, and before this age only if there was sufficient discrepancy in the paralysis in the two legs. From Stinchfield's work it had been found possible to predict with considerable accuracy the degree of discrepancy which would occur in any given case. From Green's tables it was possible to estimate the correct time to do an epiphyseal stapling of the distal femoral epiphysis of the longer limb, and this had in every case produced adequate equality of length. He therefore preferred epiphyseal stapling to leg shortening procedures if the stapling procedure could be done in time to give satisfactory correction.

### Discussion

**Mr. H. J. Seddon** pointed out that work in this country had shown that paralysis, as opposed to paresis, of muscle, could be considered final six months after the disease and in certain cases he considered it perfectly permissible to proceed with suitable tendon transplants done at about this time. He also considered that transplanting tendons into other tendons was an easier procedure and was perfectly satisfactory if well done. He agreed that fusion of the wrist should only be done with strong indications, and then only after suitable transplantations.

**Mr. H. Osmond-Clarke** agreed that muscle charts were quite useless as far as interpreting the type of operation which was necessary. He considered that surgical shortening of the longer leg was a better procedure than epiphyseal stapling.

**Mr. Donal Brooks** spoke in favour of arthrodesis of the shoulder in some cases. He also said that any attempt at transplants to provide shoulder abduction was useless unless external rotation power was present.

**Mr. Barr,** in conclusion, said that he would be happy to proceed with the tendon transplants six months after the disease if he was satisfied that matters were static. He believed that in most cases fusion of a joint should be deferred until the onset of adult life; it was an irrevocable procedure and the patient could then take part in the necessary decisions. He disliked fusion of the hip, which he did very rarely in cases of poliomyelitis, and it was indicated only when subluxation of the hip had occurred and was not amenable to stabilization by any other means. The transplant backwards of the origin of tensor fascii femoris he had found a useful operation in spastic diplegia, but not in cases of poliomyelitis.

[*December* 3, 1957]

# SYMPOSIUM ON THE TREATMENT OF ORGANIC SPINAL DEFORMITIES

OPENING papers were read by Mr. J. I. P. JAMES, Mr. H. OSMOND-CLARKE and Mr. R. ROAF; those by Mr. James and Mr. Roaf appear below.

**Mr. J. I. P. James** (London), opening the symposium, discussed the indications for surgical treatment. He first of all emphasized that the value of conservative treatment by exercises, spinal supports, &c., had never been objectively demonstrated, and in his own practice were not used. There was, however, one exception—the Milwaukee jacket. As applied to children too young for operation with rapidly progressive severe curves, this jacket could maintain a curve and even hold some correction during several years of growth.

## *The Indications for Correction and Fusion*

It should be emphasized that the great majority of those with scoliosis did not require operation because the natural development of most curves led to only a small deformity. However, there were a number, particularly those with paralytic curves, in whom a severe deformity would arise.

A distinction must be made between mature and immature curves. When the iliac apophyses had grown completely round to reach the posterior superior spine, spinal skeletal maturation was complete and the curve mature.

*Mature curves.*—Surgery did not affect the rotated ribs, usually the worst of the three parts of the deformity. In the fully grown scoliotic, therefore, consideration must be given to the amount of improvement available. The raising of a shoulder and the covering of a prominent hip were the only features which could be helped, and unless these were gross, surgery was unprofitable.

*Immature curves.*—Growing children with scoliosis nearly always had a progressive curve. This varied with the ætiology and with the various anatomical levels of curvature. The aim of surgery at this age was the correction and fusion of a curve in which the prognosis was known to be bad, in other words prophylaxis. The prognosis of the various types must therefore be known before surgery was decided upon.

## *Idiopathic Scoliosis*

There were two main factors affecting the prognosis of idiopathic scoliosis. First, the anatomical site of the primary curve; the higher the curve in the vertebral column the worse was the prognosis. Second, the age of onset; the earlier a curve appeared the worse it was at the completion of growth.

*Thoracic idiopathic scoliosis.*—The common pattern was a rapidly progressive right-sided curve seen in children after the age of 10. About half of these developed a curve of more than seventy degrees and would require surgery, especially if the curvature was fifty degrees or more by the age of 10 to 12 years.

In infants it was not uncommon to see a left-sided thoracic curve appear in the first three years of life and such a curve increased so relentlessly that curves of a hundred degrees were common in children of 5 to 7 years of age. Almost all required operation but a Milwaukee jacket could delay operation until the child was 10 years old. Before this age operation was considered undesirable, though real knowledge of the best age was lacking.

*Thoraco-lumbar idiopathic scoliosis.*—This rather uncommon curve only occasionally produced a severe curvature. The main feature was a prominent hip and occasionally even a small curve should be operated upon for this reason. Approximately 5% of these curves required operation.

*Lumbar idiopathic curves.*—None of these curves required operation for cosmetic reasons. Some later developed osteoarthritis sufficiently severely to produce pain and necessitate spinal fusion.

*Double primary thoracic and lumbar idiopathic scoliosis.*—The previously mentioned patterns had a single structural curve; this last group has two curves in opposite directions. The overall effect of such balanced curves is a good appearance and it is only in some 5% that each curve reaches one hundred degrees; it is this small group which may require correction and fusion. Unfortunately correction produces little or no improvement in the appearance, so the difficulty is making a decision before the deformities become severe. Since severe double curves are very uncommon this is a difficult task and fusion is therefore rarely indicated.

*Paralytic Scoliosis*

The outlook in paralytic scoliosis is very much worse than in the idiopathic type. Although the anatomical site of the primary curve is a very important factor in the prognosis, this is not the dominant one as in idiopathic curves. Another factor is the age at onset of poliomyelitis; the earlier it is the worse the final outlook. The third factor, and an important one, is the degree of muscle paralysis with imbalance between the two sides, particularly of the intercostals and lateral abdominal flexors. One other factor to be considered in paralytic curvature is the effect of severe but symmetrical trunk paralysis. This leads to backache, fatigue or instability, and fusion may be required for this independent of the cosmetic appearance.

*High thoracic paralytic scoliosis.*—This curvature has a very poor outlook; most of the curves develop more than one hundred degrees. The most serious cosmetic effect is the elevation of the trapezius line by the rotated transverse processes of the upper thoracic vertebræ; this is irreversible by correction and fusion. Surgery, to be effective, must clearly be undertaken before this occurs, and in the majority of cases, because most develop this serious deformity. The Milwaukee jacket is a very useful method of delaying operation.

*Thoracic paralytic curves.*—These behave in a fashion comparable to the thoracic idiopathic group, although commonly more severe. A child with a paralytic curvature of forty to sixty degrees at the age of 10 is certain to require correction and fusion before growth is complete, and it is therefore wise to undertake it early.

*Thoraco-lumbar and lumbar paralytic curves.*—These curves often become very gross and very ugly, but in such cases the child is often otherwise sadly crippled and the appearance perhaps does not matter so much. However, in many children the trunk instability is a handicap in walking, and fusion (including the sacrum if there are good hip flexors) is invaluable.

*Congenital Scoliosis*

This group is unpredictable. The great majority of children with congenital vertebral anomalies do not produce a severe curvature; many with hemi-vertebræ end up with minor kinks in their spine and there certainly is no indication for their removal. On the contrary, however, some children with congenital defects develop a curvature more severe than that seen from any other ætiology. This is particularly common when there are multiple defects over a length of six to ten vertebræ. The only way to assess a congenital scoliosis is by continued observation. Surgical intervention is called for if there is clear indication of progressive deterioration.

*Neurofibromatosis.*—10% of children with neurofibromatosis, Von Recklinghausen's disease, develop curvature. These curves are characteristically short, commonly involving five vertebræ; they are usually in the thoracic region. In the later stages kyphosis is not infrequent. The prognosis is such that all should have a prophylactic correction and fusion.

Mr. **Robert Roaf** (Oswestry):

*The Treatment of Resistant Scoliosis*

From the clinical aspect, there are four main types of scoliosis. Firstly, there is a relatively benign type which does not require any specific orthopædic treatment. This group will comprise most lumbar curves, most "double-primary", i.e. thoracic and lumbar curves, some late onset thoracic and thoraco-lumbar curves and congenital curves in which the anomaly is one or at most two hemi-vertebræ. The above curves do not usually produce severe deformities, i.e. the deformity is cosmetically acceptable and there is no serious distortion of the lungs, heart or great vessels.

By "cosmetically acceptable", I mean that the shoulders are level, a plumb line from the vertebra prominens falls within three-quarters of an inch of the gluteal cleft, and the rib hump can be masked when the patient is clothed. Recent work in the U.S.S.R. (Vilhovoy and Boyanovsky, 1957) suggests that a right-sided scoliosis carries a much worse prognosis than a left-sided scoliosis as far as distortion of the great vessels and aortic obstruction are concerned. Severe skeletal changes are compatible with satisfactory appearance and good function. This group may need encouragement and advice concerning their work, hobbies, games, dress and hair-style, but do not require splints, plasters, operations, prolonged rest or remedial exercises.

The second group consists of patients in whom the deformity is progressive and will become severe if left untreated but the curve can be corrected by conservative means, e.g. an Abbott or a Risser type of jacket, after which spinal fusion will hold the spine in satisfactory alignment.

The third group includes the flail spine in which the deformity is relatively slight in recumbency or can be easily corrected, but in whom there is gross instability and a tendency

to collapse. Such patients must either wear a cephalo-pelvic distraction brace of the Milwaukee type (Blount, 1949) or have an extensive spinal fusion.

The last group consists of patients in whom the deforming forces are very strong and in whom either correction by conservative means alone will be very difficult or, after correction and fusion, relapse will occur.

The present paper is concerned with this last group which represents only a small but important minority of all patients with scoliosis. In this group, the deforming forces are strong either because there is gross asymmetry of growth potential—as with many hemi-vertebræ, extensive vertebral hemi-fusion, multiple fused ribs or other multiple congenital anomalies, or because there is marked vertebral rotation. Whatever may have been the original cause of the deformity, once there is marked rotation deformity certain inevitable consequences result which must tend to increase the deformity (Roaf, 1958).

Firstly, the line of the centre of gravity falls to one side of the rotated vertebral bodies, tending to increase lateral curvature and inhibit growth potential on the concave side; also the longitudinal fibres of the erector spinæ muscle, whose normal action is to push the vertebræ forwards, are no longer opposed by gravity. Secondly, the long spinal muscles push the rotated vertebral bodies sideways and, as has just been pointed out, this lateral movement is unopposed by gravity. Thirdly, the balance between the deep oblique fibres of the erector spinæ muscle on the two sides is upset and their action now tends to increase the deformity. Fourthly, the deformity of the ribs is such that the respiratory movements tend to increase the deformity. Normally, the rib heads exert a balanced pressure on the sides of the vertebral bodies. In scoliosis with rotation, the pressure of the ribs on the convex side is exerted posterior to the axis of rotation, and coming on the concave side it is anterior to the axis of rotation; thus, a couple of forces is created which tends to increase the deformity at every breath.

These principles are exemplified in the treatment of four types of scoliosis—infantile scoliosis, lumbar scoliosis with lumbo-sacral instability, and thoracic and thoraco-lumbar curves with marked rotation.

*Infantile scoliosis.*—Some of these improve spontaneously; others become rapidly worse. In two children in whom the curves were becoming worse, I have managed to reverse the process by excising the spinous processes (Figs. 1A and B). The rationale of this procedure is to eliminate the rotatory action of the deep oblique fibres of the erector spinæ muscle. Clearly, such a procedure is only likely to succeed in the comparatively early case where the structural bony changes are still minimal. If there are already bony changes, more radical measures will be required (*see* following pages).



A B

FIG. 1A.—Progressive infantile scoliosis. Age 2.

FIG. 1B.—Same patient three years after excision of spinous processes.

A B

FIG. 2A.—Lumbar scoliosis with lumbo-sacral obliquity

FIG. 2B.—Same patient after stabilizing the lumbo-sacral region with an ilio-lumbar bone strut.

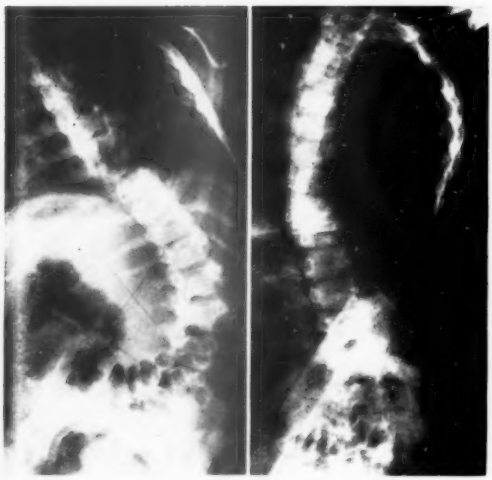
*Lumbar scoliosis with lumbo-sacral obliquity.*—Lumbo-sacral obliquity as opposed to pelvic obliquity makes correction of a lumbar curve very difficult, as the corrective force usually tends merely to increase the lumbo-sacral tilt: it is notoriously difficult to apply a corrective force directly to the apex of a true lumbar curve. It is worth noting that these curves are much uglier than ordinary lumbar curves as the whole trunk is shifted to one side. I have sometimes found it necessary to stabilize the lumbo-sacral joint with an ilio-lumbar bone strut before correcting the lumbar spine (Figs. 2A and B).

*Thoraco-lumbar scoliosis with marked rotation.*—Thoraco-lumbar scoliosis without marked rotation is a comparatively easy problem; the curve usually remains relatively mobile—at any rate for some years; conservative control during the growing period is relatively easy; conservative correction by some form of three-point pressure jacket is usually successful. After fusion, there is relatively little tendency to relapse. By contrast, if there is marked rotation the curve tends to become fixed, control and correction are difficult, and relapse after fusion is common. In fact, in the presence of marked rotation posterior interlaminar fusion in the growing period may be actually harmful, as the neural arches are tethered by the fusion but the bodies continue growing; thus the "lordosis" is increased and, owing to the vertebral rotation, this means that the vertebræ at the apex of the curve are further displaced from the mid-line.

In young patients, treatment by derotating appliances is indicated. In more advanced cases, where the curve is getting worse in spite of treatment, operative mobilisation of the spine may be required. In moderately severe cases, the main bony deformity is an asymmetry of the neural arches which are larger in all dimensions on the convex side. Adequate mobilization of the spine and correction of the deformity may be obtained by excising the interlaminar joints on the convex side.

In very severe cases, especially where the onset of deformity is early in life, a more radical procedure is required, namely multiple wedge resection of interlaminar joints and intercorporeal joints (Figs. 3A and B). This is a development of and an improvement on the original operation of massive wedge resection described by the author in 1955 (Roaf, 1955). It has the further advantage that it can easily be combined with a partial lateral vertebral epiphysiodesis by packing cancellous bone into the wedges in the bodies. If the epiphysiodesis is successful, further growth tends to correct the deformity.

Longitudinal traction and forced side bending are comparatively ineffectual methods of trying to correct these rigid curves, although they are useful where the kyphotic element predominates. Usually all that happens is that the mobile ends of the curve are corrected but the fixed central portion is unaffected, and the deforming forces which cause relapse are as strong as ever.



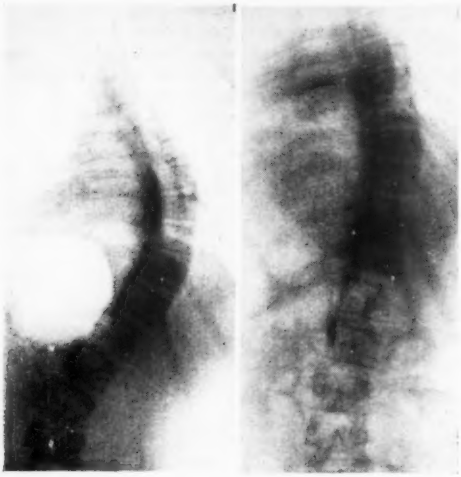
A B

FIG. 3A.—Severe progressive scoliosis due to multiple hemi-fusion. Previous conservative and operative attempts at correction had failed.

FIG. 3B.—Same patient after multiple partial epiphyseal resection.

*Thoracic scoliosis.*—Here the outward deformity is usually mainly due to the "rib hump". In the younger age group and in the less severe deformities, the curve can be controlled by either a jacket of the Abbott type or a removable splint which works on the same principle. The fundamental principle is *forward* pressure on the posterior chest wall on the convex side, *backward* pressure on the anterior chest wall on the concave side, and space for the posterior chest wall on the concave side to expand.

There is, of course, a limit to the force which can be applied to the vertebral column by external splinting. First, the skin of the trunk is relatively intolerant of continuous pressure; secondly,



A B

FIG. 4A.—Thoracic curve after attempted conservative correction.

FIG. 4B.—Same patient after lateral epiphysiodesis.

the ribs are more pliable than the vertebræ. A few years ago, I tried to derotate scoliotic spines by applying wire traction to the ribs on the concave side. I found it fairly easy to pull out the ribs and reduce the chest wall concavity but this had very little effect on the vertebral rotation.

The advantage of the Abbott principle is that pressure is intermittent, increasing with inspiration and diminishing with expiration. Such appliances must be worn for a long time and the patient must practise deep breathing. As the treatment may extend over a number of years, a removable splint is often preferable to a plaster jacket, but the underlying principle is the same. In older patients correction is more difficult, and operative mobilization of the spine as described previously may be required. (Figs. 4A and B). Finally, for mature patients with severe deformity, there are two purely cosmetic procedures which are often much appreciated by the patients, viz. partial excision of the scapula and multiple costo-transversectomy.

## REFERENCES


ABBOTT, E. G. (1911) *N.Y. med. J.*, **93,** 1217.
BLOUNT, W. (1949) *J. Bone Jt. Surg.*, **31A,** 464.
JAMES, J. I. P. (1954) *J. Bone Jt. Surg.*, **36B,** 36.
KLEINBERG, S. (1951) Scoliosis. Baltimore.
PONSETI, I. V., and FRIEDMAN, B. (1950) *J. Bone Jt. Surg.*, **32A,** 381.
RISSER, J. C. (1948) *Amer. Acad. orthop. Surg.*, **5,** 248.
ROAF, R. (1955) *J. Bone Jt. Surg.*, **37B,** 97.
—— (1956) *J. Bone Jt. Surg.*, **38B,** 640.
—— (1958) *J. Bone Jt. Surg.*, **40B,** 3.
VILHOVOY, V. F., and BOYANOVSKY, V. I. (1957) *Chirurgia*, **6,** 119.


**Mr. Denis Browne** (London), referring to infantile scoliosis, said that, in his opinion, the cases which had been described were unnecessary tragedies which could be avoided if the condition were diagnosed and efficiently treated in its earliest stage. In many respects it resembled congenital dislocation of the hip in that both conditions originate before birth, can be diagnosed in the newborn, and at this time in this country are overlooked in the vast majority of cases till the child has walked.

Though the scoliosis in the neo-nate looked very slight, its nature could be demonstrated by "triptych" X-rays which he showed, taken with the baby first lying at ease, and then bent to either side. These demonstrated the fixed nature of the scoliosis, and differentiated it from the simple wriggles so often confused with it. He suggested that orthopædics began before birth, and that the pathology of such conditions as this kind of scoliosis, congenital dislocation of the hip, talipes, and arthrogryposis would not be understood till more study was made of intra-uterine conditions. He also illustrated a splint which allowed free movement of a baby while reversing the curve of the spine, in a way that could not be done by a plaster bed.

*Proceedings of the Royal Society of Medicine*

Vol. 51
241

# Section of Proctology

President—HENRY R. THOMPSON, M.A., M.B., F.R.C.S.

[*November* 13, 1957]

## Polyposis Intestini [*Abridged*]

### PRESIDENT'S ADDRESS

By HENRY R. THOMPSON, M.A., M.B., F.R.C.S.

#### DESCRIPTION OF THE DISEASE

POLYPS may arise anywhere in the intestinal tract. They may be solitary or multiple and may result from adenomatous proliferation, inflammation or parasitic disease.

In the large intestine, multiple polypi may develop as a result of bilharzial infection or as a complication of ulcerative colitis, and the latter may be confused with adenomatous polyposis. The large intestine is the commonest place for adenomatous polypi to occur. They may appear singly, in groups of two or three, sometimes close together and at other times in widely-separated regions of the bowel, or there may be many thousands of polyps as in hereditary familial polyposis.

The question frequently arises of how many polyps must be present before the diagnosis of polyposis can be made. There is no numerical answer. The diagnosis must be based on a critical assessment of the patient's age, family history and the number and distribution of polypi. For the middle-aged patient with no family history of polyposis who has a few scattered polypi in the large intestine, the term "multiple adenomata" should be used rather than "polyposis".

The disease is characterized by hyperplasia of the glandular epithelium in the mucous membrane of the colon and rectum, resulting in the development of multiple tumours (Fig. 1). The number and distribution of the polypi vary considerably in different families and

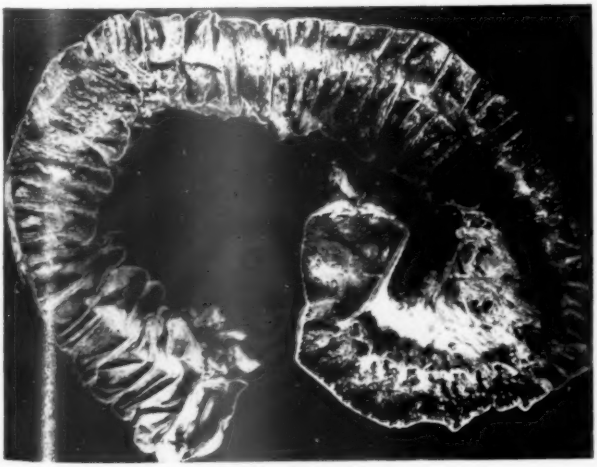


FIG. 1.—Polyposis.

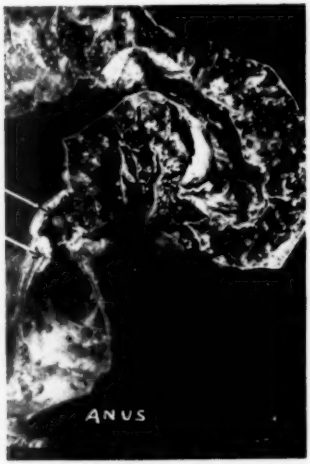



FIG. 2.—Polyposis with carcinoma.

obviously depend upon the length of time the disease has been developing before diagnosis. These tumours may be sessile and the size of a pin's head, or larger pedunculated tumours up to an inch in diameter. Of the recorded cases at St. Mark's Hospital, not one has been free of polyps in the rectum. This I regard as an important point in differential diagnosis. Moreover, although the literature states that polypi are present in the stomach in 5% of cases, I am not aware of a case of polyposis at St. Mark's having polypi elsewhere in the gastro-intestinal tract. Here I must add that gastroscopy and barium meal do not constitute part of the investigation carried out on our patients.

I should like to draw attention to a syndrome which, although reported in 1921, has remained relatively undiscussed until the last twelve years. I refer to the condition where multiple polypi occur throughout the gastro-intestinal tract, but predominantly in the small intestine. It is associated with pigmented spots on the buccal mucosa, lips and face, and sometimes on the digits of a dark-complexioned patient. The condition usually presents as an intussusception of the small intestine in the second decade of life. It is referred to as Peutz Jegher's syndrome. The condition has a familial incidence and, like polyposis coli, is believed to be transmitted as a Mendelian dominant. The clinical manifestations of the disease, however, are so different from those of polyposis coli that, apart from its genetic tendencies, it appears to be a different disease.

Although diffuse polyposis has been reported in an infant, polypi start to develop, as a rule, about the age of puberty. They give rise to symptoms at the age of 20, and fifteen years after the onset of symptoms the polypi start to turn malignant. Cancer will develop by the age of 35, some twenty-five years earlier than the development of carcinoma of the large intestine in the general population (Fig. 2).

The first symptom is diarrhœa and this is unlikely to start until a considerable number of polypi have developed. At its onset it is so slight and its progression is so slow that changes in stool consistence and bowel habit may go unnoticed by the patient. It is remarkable the number of polypi that can develop and the extent of the bowel involved in a patient who denies any symptoms. Eventually, the increasing diarrhœa, with the occurrence of hæmorrhage and mucous discharge, interferes with the patient's daily life and leads to deterioration of his general health.

## Genetics

Polyposis coli is a hereditary disease and is passed on through families from one generation to the next. The units of hereditary transmission are genes which occupy fixed positions in the chromosomes and are probably large, single protein molecules. It is at present believed that hereditary diseases are the result of gene mutations. Some of these diseases, such as hæmophilia, are present at birth. Polyposis, on the other hand, develops at puberty—a characteristic it shares with hereditary optic atrophy. Polyposis affects both males and females and can be transmitted by both sexes but only those who have inherited polyposis can transmit it to the next generation. Half of the children in such families will inherit the disease.

Investigation of a family with this disease starts with the diagnosis of polyposis in an affected member. At the time of diagnosis enquiries may produce evidence of the disease in other members of the family. The preliminary interviews with the family should be made with the object of selecting a "collaborator", embued with what Dr. C. Dukes has so aptly described as the "tribal outlook", or someone who knows all the family affairs—usually a "she".

Once a collaborator is established, there is a chance of keeping in contact with family members.

## Treatment

The problem of the treatment of a case of polyposis involves the treatment of an individual with the disease, and the little group or community of people that constitute the family. It is essential that the treatment of the first sufferer in a family should, if possible, be free from anxiety and complications. This is the talisman for winning the confidence of the family itself.

The only effective treatment known at present is surgical removal of the large intestine. This is commonly practised in one of two ways—total removal of the large bowel with permanent ileostomy, or subtotal removal of the large bowel with preservation of a rectal stump and restoration of continuity of the bowel.

(1) *Total removal of the large bowel.*—The disadvantage of this operation is that the patient is left with a permanent ileostomy with the recurring trouble of ileostomy appliances, and the risk of ileostomy complications, as well as the complications that may arise from excision of the rectum, such as impotence in the male. The advantages are that it removes all risk

of malignancy, and check-ups are not required. It is the only treatment if a carcinoma is present in the rectum, and indeed many consider that it is indicated should malignancy be present in any part of a colon affected with polyposis.

(2) *Preservation of the rectal stump.*—The advantages of preserving continuity of the bowel are obvious. The disadvantages are the risk of malignancy and the necessity of a six-monthly check-up on the rectal stump for the rest of the patient's life. Admission to hospital may be required for fulguration and a second major operation may be necessary to remove the rectum.

What is the risk of malignancy developing in the rectal stump? Light can be thrown on this subject in two ways—from our knowledge of where carcinoma occurs in malignant polyposis, and from the number of cases that subsequently develop a carcinoma in the retained rectal stump.

Of 70 patients operated on at St. Mark's Hospital for polyposis, 30 had already developed a carcinoma of the large bowel at the time of treatment. In 23 of these 30, malignant change had taken place in the rectum. From this it would appear that the rectum is the commonest place for a carcinoma to develop and it is this segment of the large bowel, if any, that should be removed.

A statistical study of the occurrence of a carcinoma in the rectal stump following ileo-rectal anastomosis is at present not possible because there are no sufficiently long follow-up records available after this operation. Of cases treated by preservation of the rectum at St. Mark's, 3 are known to have developed a carcinoma in the rectal stump, two, sixteen and twenty-one years after operation; a case of Mr. H. Edwards' developed a carcinoma ten years later.

The literature would suggest that at the moment the incidence is between 5% and 8% but with the passage of time I feel sure this figure will increase.

The argument in favour of retaining a rectal stump and restoring continuity of the bowel rests on the supposition that if a carcinoma develops it will start as a malignant change in an adenoma and that this change can be prevented by keeping the rectal stump free from polypi by six-monthly examinations and fulgurations. Against this it must be pointed out that a carcinoma may develop *de novo* from rectal mucosa without the intervening stage of a polyp; and either patient or surgeon may default on the six-monthly check. At these follow-up examinations the rectum frequently contains fæcal material and a thorough examination is not possible unless the bowel is prepared. Moreover, a break in supervision may result from the surgeon retiring or dying. It is easy to talk about regular checks and keeping the rectal stump free from polyps but it is a different matter to achieve in practice.

Thus it would appear that the more radical operation is safer for the patient and easier for the surgeon. There is, however, a human side to this problem. First, patients with polyposis are young people, some of them without symptoms. A surgeon needs considerable powers of persuasion to coax such people to submit to a permanent ileostomy with all the adjustments and changes in relationship that this entails. One does not need a vivid imagination to understand a young girl's fear that a man's encircling arm would encounter an ileostomy bag. The chances of marriage are reduced for a person with an ileostomy although at least two cases come to mind where young girls with ileo-rectal anastomoses have married and had children.

The choice lies between a normal life in one's "salad days" with the risk of cancer eventually developing in the rectal stump to shorten the normal expectation of life—contrasted with an ileostomy with its restrictions, but with the chance of a normal expectation of life. It is my experience that youth will accept the risks of an ileo-rectal anastomosis in preference to the security of an ileostomy.

An attempt at a compromise can be found in the ileo-anal operation, or anal ileostomy. In this operation, the muscle walls of the rectal stump are retained but the mucosa is removed and replaced by a length of ileum.

## Operative Details

I now propose to discuss the three operations practised to-day in the treatment of polyposis of the colon.

(1) *Proctocolectomy.*—This is best done in one stage and can be expeditiously performed by two surgeons working simultaneously, with the patient in the lithotomy Trendelenburg position. The time required to complete such an operation need not be more than an hour and a quarter. The patient will be ready to leave hospital in twenty-five days.

(2) *Colectomy and ileo-rectal anastomosis.*—This resolves itself into three phases:

(*a*) clearing the rectal stump of polypi;

(*b*) excising the colon and anastomosing the ileum to the rectum;

(*c*) subsequently keeping the rectum free from polyps.

The first phase is best managed in a series of monthly fulgurations, systematically and deliberately ridding the rectum of polypi to a distance of 15 cm. from the anal margin. The second phase is again best performed in the lithotomy Trendelenburg position. The advantage of this position is that an assistant can pass a sigmoidoscope from below after the rectum has been transected and the rectal mucosa can be carefully searched for residual polypi which should be fulgurated (Figs. 3, 4). The ileum should be divided as close to the

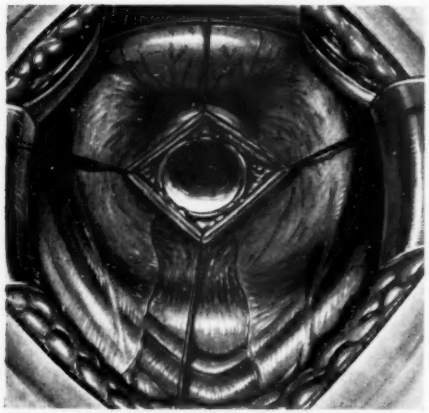


FIG. 3.—Abdominal view of sigmoidoscope passed into rectal stump, preparatory to fulguration of residual polypi.

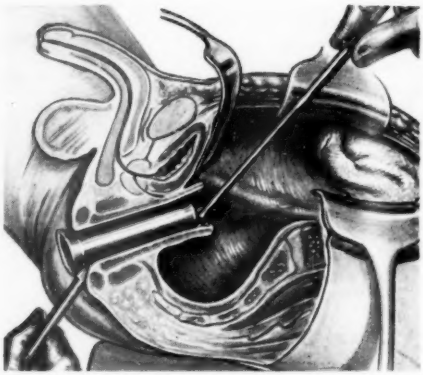


FIG. 4.—Combined clearing of rectal stump of residual polypi.

cæcum as possible for not only does it widen out near the ileo-cæcal valve, but subsequent function seems better if this portion of ileum is preserved. There is always disparity in size between the smaller ileum and the larger rectum but an end-to-end anastomosis can usually be achieved by careful "tailoring". An alternative and satisfactory procedure is to anastomose the side of the ileum to the end of the rectum, thereby perhaps achieving a wider stoma but adding the risk of a sutured blind end. From the point of view of subsequent examinations and the risk of malignant change, obviously, the shorter the rectal stump the better. I prefer to divide the rectum 2·5 cm. above the peritoneal reflection and leave a rectal stump of some 10 to 12 cm. The function of such an ileo-rectal anastomosis is satisfactory. In the months after operation the motions are loose and the bowels are open five to six times a day with an occasional action at night. This settles down and the patient finally has two formed motions in twenty-four hours.

(3) *Ileo-anal anastomosis.*—This procedure is the same as for an ileo-rectal anastomosis except that, following division of the rectal stump, the rectal mucosa is dissected or "cored out". In this procedure two points are of assistance: (1) submucosal injections of saline in adrenaline (20 minims 1/1,000 adrenaline in 4 oz. saline), and (2) to secure the necessary tension in the submucosal stripping plane a catheter is passed up the rectum from below. The cut edge of the mucosa is tied to the end of the catheter and the mucosa is pulled down as it is dissected out. When the mucosa has been removed the ileum is threaded through the remaining muscular tube and sutured to the anal canal. The lithotomy Trendelenburg position is essential for the use of the catheter and for the suturing of the ileum to the anal canal (Fig. 5).

(Details were given of a boy of 17 and a girl of 16, whom the speaker treated by an ileo-anal anastomosis, who were followed up for four years.)

Cases with satisfactory function following ileo-anal anastomosis have been reported in the literature, notably by Devine and Webb, and this method merits trial where indicated.

In my cases it was considered that the ileum separated from the anal canal and retracted to the top of the rectal stump where it was firmly held by interrupted seromuscular sutures. The bare rectal tube finally became epithelialized (Fig. 6).

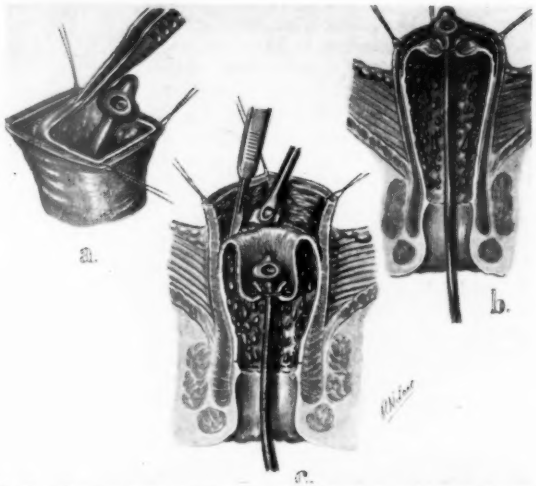
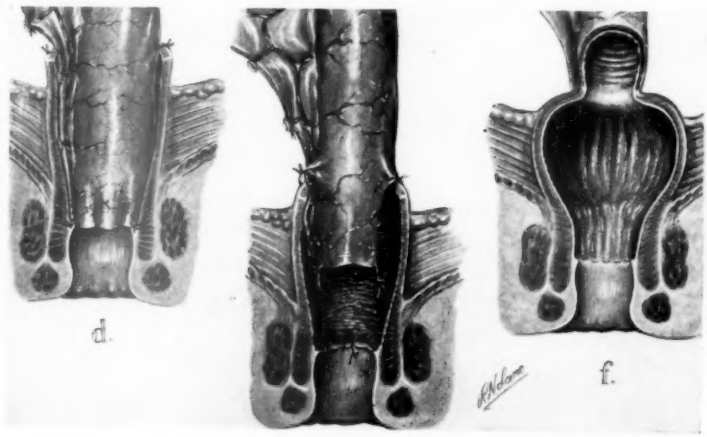



FIG. 5.—Method of coring out anal mucosa. a, Catheter inserted in rectal stump. b, Cut edge of mucosa tied to catheter. c, Traction on catheter aiding dissection of mucous membrane.




e.

FIG. 6.—Diagrammatic representation of probable result of author's two cases of ileo-anal anastomosis: d, anastomosis completed. e, breakdown of anastomosis and retraction of ileum to top of muscular rectal stump. f, re-epithelialization of rectal stump.

It is more than a coincidence that each of these cases has had a post-operative intestinal obstruction. This complication is unpleasantly frequent in abdominal operations where raw areas and ligated pedicles are left in all four quadrants of the abdomen. Because of the adherence of retained omentum to loops of small intestine, I think that it is better to remove it

I would here like to give credit to Dr. Cuthbert Dukes, for it is mainly due to his efforts and organizing ability that 57 families, embracing 700 members (250 affected by

polyposis) have been documented at St. Mark's, and his papers on the subject stand out as landmarks.

BIBLIOGRAPHY

AYLETT, S. O. (1952) *Proc. R. Soc. Med.*, **45**, 394.
BACK, I. (1913) *Proc. R. Soc. Med., Sect. Surg.*, **7**, 193.
CLARK, E. A. (1929) *Proc. R. Soc. Med.*, **23**, 713.
DEVINE, J., and WEBB, R. (1951) *Surg. Gynec. Obstet.*, **92**, 437.
EDWARDS, S. (1910) *Proc. R. Soc. Med., Sect. Surg.*, **4**, 99.
ELLIS, R. W. B. (1938) *Proc. R. Soc. Med.*, **31**, 1048.
GABRIEL, W. B. (1936) *Proc. R. Soc. Med.*, **29**, 1008.
—— (1951) *Proc. R. Soc. Med.*, **44**, 198.
LEWIS, E. E. (1941) *Proc. R. Soc. Med.*, **34**, 558.
LOCKHART-MUMMERY, J. P. (1919) *Proc. R. Soc. Med., Sect. Surg.*, **12**, 43.
MAKINS, G. H., WALLACE, C., and SARGENT, P. (1912) *Proc. R. Soc. Med., Sect. Surg.*, **5**, 137.
NEWBOLT, G. P. (1914) *Proc. R. Soc. Med., Sect. Surg.*, **7**, 272.
NORBURY, L. E. C. (1928) *Proc. R. Soc. Med.*, **21**, 1441.
—— (1930) *Proc. R. Soc. Med.*, **24**, 198.
—— (1933) *Proc. R. Soc. Med.*, **26**, 1054.
ROWNTREE, T. (1950) *Proc. R. Soc. Med.*, **43**, 686.
WATSON, C. G. (1913) *Proc. R. Soc. Med., Sect. Surg.*, **7**, 194.

[*January* 8, 1958]

**Ileo-Cæcal Tuberculosis.**—H. R. THOMPSON, F.R.C.S., and B. C. MORSON, D.M.

Mrs. E. D., aged 71.

*History.*—Admitted to hospital with subacute intestinal obstruction after one month's history of indigestion, diarrhœa and loss of weight. No family history of tuberculosis.



FIG. 1.—Specimen showing ileo-cæcal tuberculous ulceration. Patient Mrs. E. D., aged 71.

Operation revealed a constricting growth of the ileo-cæcal region with enlarged regional lymph glands. Liver clear. Right hemicolectomy with end-to-end anastomosis.

*Pathology Report.*—Terminal ileum with the cæcum and ascending colon (Fig. 1). The terminal two inches of ileum and ileo-cæcal valve show ragged ulceration. The ileo-cæcal lymph glands are moderately enlarged and a part of the surface of the mesentery has a granular appearance.

*Histology.*—Sections show numerous caseating giant cell systems in the bowel wall. The regional lymph glands also contain similar tissue. Part of the surface of the mesentery is covered by miliary deposits.

Sections stained for tubercle bacilli show large numbers of organisms in the bowel wall but only a few in the regional lymph nodes.

**Two Unusual Cases of Recto-sigmoid Carcinoma with Bladder Involvement.**—A. N. SMITH, F.R.C.S. (for H. R. THOMPSON, F.R.C.S.).

I.—Mr. J. S., aged 22, agricultural student, was admitted to hospital on 17.9.57, with one year's history of diarrhœa with blood and mucus in the stools, loss of weight and severe dysuria. *Sigmoidoscopy* showed a carcinoma at 11 cm. Biopsy proved this to be a



FIG. 1.—Specimen of advanced carcinoma of rectum invading base of bladder and prostate.

adenocarcinoma of average grade of malignancy. *Cystoscopy* showed a bullous cystitis and extrinsic pressure on the vault of the bladder. *Laparotomy* disclosed four carcinomas in the large bowel—in the cæcum, transverse colon, recto-sigmoid and rectum. The recto-sigmoid lesion was attached to the bladder and left ureter with a recto-vesical fistula. Procto-colectomy and ileostomy (Mr. H. R. Thompson and Mr. H. E. Lockhart-Mummery) with partial cystectomy and ureteroureteric end-to-side anastomosis was performed. The patient made a satisfactory recovery with good function on an I.V.P. and a blood urea of 22 mg.%.

II.—Mr. H. H., aged 52, a sewerman, had a six months' history of diarrhœa and dysuria. He had a carcinoma of the rectum, lower edge at 5 cm., spreading down from the upper rectum and involving the prostate and bladder. Average grade adeno-carcinoma (Fig. 1). Excision of the rectum with pelvic clearance and the formation of an ileal bladder was performed (Mr. H. R. Thompson and Mr. H. E. Lockhart-Mummery). His condition was satisfactory on discharge from St. Mark's Hospital. His blood urea was 28 mg.%.

**Diverticulitis of Colon.**—BRUCE BOMFORD, F.R.C.S. (for HAROLD DODD, F.R.C.S.).

Mrs. K., aged 52. She had not walked since the age of 4 years when she had poliomyelitis affecting both legs.

*Present complaint.*—Spasms of pain in left lower abdomen with constipation for six months.

*On examination.*—Mobile mass in left iliac fossa. Opaque enema not retained; normal pyelogram; Hb 52%.

*Operation.*—Resection of mass from pelvic colon with end-to-end anastomosis.

*Specimen.*—Chronic abscess cavity encircling colon with easily seen fistulous communication to the lumen.

*Discussion.*—Case showing one of the several presentations of diverticulitis, e.g. mass clinically suggesting neoplasm. Other clinico-pathological types mentioned included acute inflammatory mass, fibrosis with intestinal obstruction and massive hæmorrhage.

**Crohn's Disease and Colitis.**—C. I. COOLING, F.R.C.S. (for RONALD W. RAVEN, O.B.E., F.R.C.S.).

A subtotal colectomy specimen was shown from a girl of 20 with a history of attacks of abdominal pain and diarrhœa for ten years. The barium studies suggested a diagnosis of Crohn's disease of the colon with an internal fistula.

The specimen revealed marked thickening of the terminal ileum with macroscopic features typical of Crohn's disease, but in the ascending and transverse colon there was extensive ulceration with pseudopolypoidal mucosa, appearances typical of ulcerative colitis. Histological preparations revealed giant and epithelial cells in granulomatous follicles as in Crohn's disease.

A comparable colon specimen of typical ulcerative colitis from a girl of 19 also showed follicles in the wall of the bowel with numerous giant cells present. Discussion on the relationship between the two diseases then followed.

**Crohn's Disease of the Rectum.**—H. W. A. BARON, F.R.C.S.

Mrs. I., aged 68.

The diagnosis of Crohn's disease in this elderly woman was made by biopsy. She presented with a two months' history of diarrhœa with slime. There was a palpable infiltrated lesion in the rectum. Sigmoidoscopy showed a stricture at 13 cm. and a barium enema showed a filling defect suggesting carcinoma. Her symptoms completely settled down without treatment. She now has one normal stool a day but despite this, changes of

granular proctitis, which were not present when she was first seen, have now developed in the rectum below the stricture. No evidence of tuberculosis was found on full investigation. A guinea-pig was inoculated with the biopsy material and no macroscopic or microscopic evidence of tuberculosis found although every organ and the inoculation site were sectioned.

**Ano-rectal Melano-sarcoma.**—FRANK FORTY, F.R.C.S.

H. H., female, aged 65.

*History.*—Painful swelling in right groin for three days.

*On examination.*—Enlarged glands in both groins. At anus several discrete firm purplish polypoid nodules extending towards the rectum and with black pigmentation spreading diffusely into the adjacent peri-anal skin.

*Operation* (17.12.57).—Abdomino-perineal excision of rectum and bilateral removal of inguinal glands. There were no obvious intra-abdominal metastases. Uneventful recovery.

Microscopically the primary growth and the inguinal glands all showed malignant melanoma with numerous mitoses and much pigment.

*Comment.*—A rare condition with a bad prognosis.

Dukes and Bussey (1947) reported 2 cases and Raven (1948) reported 3 cases, and reviewed the literature which at that time recorded only about 100 cases.

REFERENCES

DUKES, C. E., and BUSSEY, H. J. R. (1947) *Brit. J. Cancer*, **1**, 30.
RAVEN, R. W. (1948) *Proc. R. Soc. Med.*, **41**, 469.

**Lymphosarcoma of Rectum.**—H. GORDON UNGLEY, F.R.C.S.

Mrs. B., aged 66. Admitted to Gordon Hospital, 8.5.57.

This patient presented with a feeling of incomplete evacuation of the bowels for twelve months, with occasional recent bleeding. No loss of weight.

A broad, pedicled swelling was palpable 5 cm. from the anus. Proctoscopy confirmed a sessile polyp, $5 \times 2{\cdot}75$ cm., covered by smooth but invaded mucosa.

Biopsy revealed it to be a lymphosarcoma but, unlike most of these tumours, there was no palpable induration extending up the bowel from the tumour, nor was there other evidence of dissemination.

It seemed, therefore, that this was a case available for treatment much earlier than is usual and, with a radical operation, perhaps a cure might be achieved. At the abdomino-perineal excision in May 1957 there was, in fact, no evidence of extension or dissemination of the growth.

The tumour consisted of sheets of lymphocytes without follicular arrangement invading and ulcerating the mucosa and submucosa but not involving muscle coats. Occasional mitoses were present. Because of its structure and pattern this tumour must be considered a lymphosarcoma.

In the lymph nodes examined the remains of follicles could be seen and the pulp was filled with mature lymphocytes and it was impossible to say whether this was metastatic infiltration or not.

**Polyposis Coli with Several Areas of Carcinomatous Degeneration.**—R. V. COOKE, Ch.M.

S. C., male, aged 50.

Admitted to Bristol Royal Infirmary, 16.11.57.

*History.*—He was well up to July 1957, when he noticed blood *per rectum* and occasionally slime. He had lost almost one stone in the last three months, but otherwise felt fit. He had never had any intestinal symptoms before this, except that his bowel movements had always been rather loose, and that twelve years ago he had passed a few blood-stained motions which lasted for one or two days only.

*On examination* (18.11.57).—Multiple polyps from the anal margin up to 20 cm. Harder nodules were palpable on the posterior wall of the rectum 2·5 cm. from the anus, and one hard mass a few inches higher up.

Biopsies were taken from four polypi. All proved malignant and showed well-differentiated adenocarcinoma. No signs of inflammation or ulcerative colitis or dysentery.

*Barium enema.*—Extensive polyposis of the left half of the colon to the anal margin with two greater irregular filling-defects on the posterior wall of the rectum and at the junction of the descending colon and sigmoid, these being the malignant degeneration of the polyps. From the X-rays it looked as if most of the transverse colon and the ascending colon were normal.

*Abdomino-perineal excision of rectum and removal of descending colon* (28.11.57).—Further resection deferred because much time was required to mobilise a growth in the pelvic colon which had obstructed the bowel so that the proximal colon was full of fæces.

A colostomy was made through the abdominal incision.

Following the operation he progressed, although the transverse colon at the colostomy was crowded with polypi.

*Pathological report.*—"The specimen shows papillomatosis (polyposis) of the whole colon. There is a carcinoma (6×3·5 cm.) 2 cm.; and another (5×6 cm.) 6 cm.; and a small ulcer also probably malignant 8 cm. above the anal margin. The neoplasm is a Grade II type adenocarcinoma which extends beneath the normal mucosa and is invading the muscle coats but did not reach the serous coat. The lymph gland did not show evidence of malignancy. The rest of the polypi were the ordinary ones seen in congenital multiple polyposis."

On 6.1.58 the remainder of the transverse colon and the ascending colon was excised. A proximal right transverse colostomy had to be abandoned, since there were polypi everywhere. The ascending colon and cæcum were studded with innumerable polypi. The appendix was unaffected and none was felt in the small bowel.

*Remarks.*—This case was shown as complementary to our President's address on Polyposis Coli. It merits reporting in view of the age of the patient (50) and that he had lived fifty years with so few symptoms. We were unable to find a case older than 43 in the literature. In the discussion Dr. Cuthbert Dukes agreed that the specimen with many malignancies was typical of familial polyposis coli. The absence of other cases in the family was interesting but, he said, the disease must have a fresh beginning somewhere.

It was a pity that the rectum had to be sacrificed, but its malignancy extended too low to preserve it. The man seemed undistressed by his ileostomy and is about to return to work (February 7, 1958).

*Comment.*—This patient was the only member of his family of 5 brothers and 4 sisters to be affected. His father died at 51 years of chronic hepatitis. His mother died aged 50, of some other disease. The patient's grandparents were not affected but the family was known to have "liver trouble".

**Complete Rectal Prolapse Following Operation for a Tumour of the Cauda Equina.**—E. C. B. BUTLER, F.R.C.S.

Woman, aged 33.

1947: Laminectomy and removal of neurofibromata from cauda equina (Mr. D. W. C. Northfield).

Following this operation: Gradual onset of complete rectal prolapse and incontinence of urine. The latter was treated successfully by Professor V. W. Dix.

February 1953: Admitted to the London Hospital with enormous rectal prolapse.

*Laparotomy* (11.2.53).—Pelvic colon and rectum mobilized, with excision of peritoneal pouch between rectum and vagina. Recto-sigmoidectomy carried out from below, about 1 ft. of bowel being removed. The pelvic floor was reconstituted at a higher level. Abdomen closed.

One week later patient had a severe secondary hæmorrhage, emergency colostomy was performed, which was closed five weeks later.

Patient has been well for four years and has had no recurrence of the prolapse.

Last year she became pregnant and had a Cæsarean section.

**Pneumatosis Cystoides Intestinalis.**—HAROLD C. EDWARDS, C.B.E., M.S.

Man, aged 52. In 1943 perforated duodenal ulcer repaired, since when he has suffered recurrent attacks of duodenal ulcer pain. A barium meal in 1953 showed a stenosing duodenal ulcer. A "straight" X-ray of the abdomen showed gas under the right dome of the diaphragm.

*Operation* (10.7.53).—Many thin-walled transparent cysts under the serous coat of the small bowel and in the mesentery, varying in size from a pin's head to ¾ in. in diameter. About 12 in. of jejunum together with the larger mass of cysts was resected. Gastro-enterostomy. Uneventful recovery. Patient in fair health. On analysis, the gas in the cysts proved to be air. The wall of the cysts consists of a single layer of foreign body cells, with many lymphocytes and plasma cells.

**Idiopathic Gangrene of the Colon.**—B. J. FOWLER, F.R.C.S. (for H. BLACOW YATES, F.R.C.S.).

A 67-year-old housewife previously quite well was seized with severe persistent abdominal pain at 4 a.m. There was neither vomiting nor bowel action. The abdomen was flat, tender, rigid and silent. The pulse was regular. Laparotomy at 12 noon showed the colon to be gangrenous from the ileo-cæcal region to the lower pelvic colon. It was resected. Uneventful recovery followed. Later sigmoidoscopy showed no abnormality. Multiple sections of the vessels showed no thrombosis or embolism. Section of the colon showed necrosis mainly limited to the mucosa.

No member present had seen a similar case. A streptococcal causation was mooted.

**Localized Benign Ulceration of the Colon with Unusual Features.**—J. A. LLOYD DAVIES, M.B., B.S., F.R.C.S.

This ulcer (Fig. 1) was removed from the middle of the transverse colon of a diabetic woman aged 55 with a proctosigmoiditis of fifteen months' duration. For the last three months she has shown the clinical features of a severe ulcerative colitis. There were five additional similar discrete ulcers in the descending colon and one in the cæcum, but the remaining colon was normal. The histological changes are those of an ulcerative colitis, unlike the macroscopic appearances which show a sharp ulcer margin and normal surrounding mucosa. A focal arteritis is seen at the margin of the ulcer (Fig. 2), and an alternative diagnosis of necrotizing arteritis due to polyarteritis nodosa was suggested. Symptomatic recovery followed transverse colostomy and has been maintained for over a year, although some proctitis persists.



FIG. 1.—Benign ulcer of the transverse colon, with normal surrounding mucosa, from a patient with clinical features of a severe ulcerative colitis.



FIG. 2.—Section from the margin of the ulcer showing submucosal arteritis. →

# Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

[*December* 11, 1957]

## DISCUSSION ON NON-ARTICULAR RHEUMATISM

**Dr. B. G. B. Christie** (London):

No recognized classification of non-articular rheumatism has yet been established. In the past many of these conditions were described as "fibrositis", but more recent evidence reveals that this condition does not exist. The late Sir William Gowers (1904) labelled as "fibrositis" the changes which were thought to be present in fibrous tissue and which in their turn were the cause of the numerous aches and pains to which man is heir. The picture was clouded further by Stockman (1920), who described the changes of chronic inflammation in white fibrous tissue, a histological finding that has not been confirmed notwithstanding the innumerable biopsies that have been carried out.

Some of the pains previously ascribed to fibrositis tend to affect the mid-line posteriorly radiating out along the shoulder and pelvic girdles. Much of this pain arises from articular lesions in the spine itself, although in a small number of cases described by Copeman (1949) the pain has been shown to arise from herniated fat nodules. These may represent some of the fibrositic nodules or "trigger spots" that were commonly described in the past. The fibrositic nodule that may be felt beneath the skin, but which is so elusive at the time of biopsy, is probably a local muscle spasm, which may be a manifestation of referred pain.

### CLASSIFICATION

The only satisfactory classification of non-articular lesions must be on an anatomical basis, and the classification of Slocumb (1943) albeit of fibrositis is a useful beginning. This classification is:

(1) Intramuscular (myositis, "muscular rheumatism").
(2) Periarticular.
(3) Tendinous or fascial.
(4) Perineural.
(5) Bursal.
(6) Panniculitis.

To this I should like to add a seventh, namely

(7) Of bony origin.

(1) *Muscular Lesions*

Lesions in muscle are diagnosed because the muscle feels either doughy or hard to the touch and is tender on handling. Contraction of muscle will give rise to pain, and this may be elicited by active movement of the muscle and aggravated by resisted movement. Muscle pain is usually deep in character and defies accurate localization. Any lesion arising in muscles will then have these characteristics.

Patients frequently complain of pain following exposure to cold and dampness for which we still lack a satisfactory explanation.

Inflammation of muscle may be either (*a*) suppurative or (*b*) non-suppurative. (*a*) Suppurative lesions are rare and may be either primary or secondary to pyæmia and septicæmia. Primary myositis may be due to infection by staphylococci, streptococci or the organisms of gas gangrene associated with direct trauma. Secondary lesions are usually due to the chronic granulomata such as tuberculosis, actinomycosis and syphilis.

(*b*) Non-suppurative myositis is not uncommon and includes such conditions as fibrosing and ossifying myositis. In progressive myositis fibrosa the complaint is of stiffness more than pain, and the shortening of the muscles due to the fibrosis often gives a picture that resembles a symmetrical Volkmann's contracture of four limbs.

Myositis ossificans occurs in three clinical forms. *The first clinical type* is the classical ossification that takes place in the attachment of a muscle, such as that giving rise to the "rider's spur" at the insertion of the adductor muscles of the thigh.

*The second clinical type* is that occurring in the belly of a muscle usually as the result of direct trauma giving rise to a hæmorrhage, eventual calcification taking place. This type is called myositis ossificans circumscripta to differentiate it from the *third clinical*

*type*, progressive myositis ossificans, which differs from progressive myositis fibrosa only in the calcification that is seen in affected muscles. Pain is not so prominent in this group of conditions as tenderness and stiffness.

Tenderness of muscles is a feature of peripheral neuritis of whatever cause and is also associated with subacute combined degeneration of the cord. The neurological findings in these cases should direct attention to the primary lesion which usually overshadows the element of painful muscles.

Myositis is commonly seen in the so-called "collagen" diseases or with neoplasia especially carcinoma of the bronchus. In dermatomyositis the muscle element may precede or appear entirely separate from any dermatological involvement. When it does so the complaints are of vague aches and pains referable to muscles which themselves are weak and frequently tender to the touch. Palpation may reveal them to have the characteristic "doughy" consistency.

Recent studies in electrodiagnosis have shown that in many of these cases of dermatomyositis or polymyositis there is a characteristic picture, which may be of assistance in early diagnosis.

Intensity duration curves on the affected muscles often show varying evidence of denervation and when this is prominent the condition may be termed dermatoneuromyositis or polyneuromyositis. On electromyographic exploration spontaneous activity in the form of fibrillation or positive potentials will be seen when there is evidence of denervation on intensity duration curves. On volition there is a pattern which is compounded of potentials of less than one millivolt in amplitude, and less than one millisecond in duration. The affected motor units proclaim the dearth of active muscle fibres by the production of a crackly note on the loudspeaker and by assuming many of the appearances of a classical myopathy. The difference from the latter, however, is in the incomplete pattern, namely there is a qualitative decrease bearing a direct relationship to the degree of denervation present. A further characteristic finding is that samples from different points in the same muscle may produce a pattern that is both quantitatively and qualitatively normal.

About 10% of cases of polyarteritis nodosa are complicated by peripheral neuritis and it may be the presenting lesion. It is classically asymmetrical and in addition there is often pain in the limbs and muscle tenderness. Electrodiagnostically the findings associated with the peripheral neuritis do not segregate it from that due to other causes.

In scleroderma, or systemic sclerosis, the presenting symptom is frequently one of muscular pain leading the patient to diagnose his condition as "rheumatism". Further developments, such as tightness of the skin or dysphagia, usually eventually point to the correct diagnosis in this distressing condition.

Focal lesions of collagen occur in the muscles in systemic lupus erythematosus but the more florid manifestations of the disease will overshadow the muscular involvement. Many of these collagen diseases respond well to steroid therapy; in polymyositis and dermatomyositis marked clinical improvement has been paralleled by a return of the electrodiagnostic findings to normal after giving steroids in high dosage.

Myalgia has been reported in the scleroderma of Buschke (1900) but here again the œdema of the skin and its "hidebound" appearance are unlikely to make one think in terms of a primary muscle pathology.

Trichiniasis causes acute muscle pain when the infestation is severe and there is usually an associated eosinophilia. The muscles most commonly affected are the deltoid and gastrocnemius. It is important to differentiate trichiniasis, which causes acutely painful muscles five to seven days after infestation due to the migration of the larvæ of *Trichinella spiralis*, from cysticercosis of muscle which affects the same anatomical sites but is painless and only the cysticerci of *Tænia solium* are visible on X-ray due to their calcification.

Muscular aches and pains are frequently seen in endocrine disorders particularly acromegaly and myxœdema. In the former the facies and general appearance will probably disclose the diagnosis, but in myxœdema patients often complain of vague aches and pains related both to joints and muscles before their appearance is frankly myxœdematous.

In rheumatoid arthritis itself the involvement is widespread and frequently muscular aches and pains may be as troublesome to the sufferer as the joint lesions.

Muscle cramps occur in a large number of medical and especially neurological conditions. Special mention, however, should be made of muscle cramps that follow intervertebral disc lesions, especially those in the lumbar spine. These patients often suffer from night cramps in a leg that has previously been the seat of sciatica and it is interesting to note that the muscle group involved is frequently the one that was the site of the most severe pain at the time of the acute lesion. In my own experience I have found that the onset of these cramps frequently has a favourable prognosis in that it heralds the period of regression of the sciatic pain. Fortunately the cramps respond well to oral calcium lactate or to quinine.

(2) *Periarticular Lesions*

The main periarticular lesion to cause pain is capsulitis of the shoulder. Because there is capsular involvement there is of necessity limitation of movement in all directions. An interesting condition associated with capsulitis and occasionally missed is the shoulder-hand syndrome of Steinbrocker (1947). In this there is swelling and stiffness of the hand and forearm with skeletal rarefaction simulating Sudek's atrophy but without joint involvement. If the shoulder lesion is missed a mistaken diagnosis of rheumatoid arthritis in the hand is likely to ensue.

(3) *Tendon and Fascial Lesions*

In the third group are those conditions of tendinous or fascial origin. Tendinous lesions can only occur at those sites where well-developed tendons exist and these are mainly in the region of joints. Because of this proximity to the joints many pains arising from the tendons or their sheaths are incorrectly assumed to arise from the joint itself. The main site for tendon lesions in the lower limb is around the ankle-joint, and in the upper limb in the hand and wrist and to a lesser extent the shoulder. The commonest affection of tendons is a tenosynovitis, and the position of this inflammation is determined by anatomical considerations such as fibro-osseous tunnels or fibrous bridges, through or under which the tendons pass.

Tenosynovitis is of common occurrence in rheumatoid arthritis especially in the flexor tendons of the fingers. Because of its association with the joint disease the inability to flex the finger is often attributed to the arthritis of the interphalangeal joint. A simple test may be performed to differentiate these two. In the case of an arthritis of an interphalangeal joint flexion both active and passive is limited to the same extent and by pain. In tenosynovitis active flexion is limited and painful but passive flexion is full and painless because the tendon is not being called upon to move within its inflamed sheath. In many of these cases it is possible to palpate the thickened nodular tendon usually on the volar aspect of the metacarpal head.

There are four cardinal signs of tenosynovitis at any site:

(1) Pain on active movement of the tendon.
(2) Increased pain on resisted movements.
(3) Pain on passive stretching of the tendon in its sheath.
(4) Pain on palpation over the inflamed part of the tendon.

By applying these simple tests it is possible to determine the exact tendon sheath that is involved. This is now of great practical importance because of specific treatment with hydrocortisone. All the six tendon sheaths on the dorsum of the wrist must be examined individually in pain at this site to determine which one is affected, similarly one must examine the flexor pollicis longus, common flexor sheath and flexor carpi ulnaris in pain on the flexor aspect.

Textbooks frequently draw attention to the tenosynovitis of the common flexor sheath being tuberculous in origin. This is undoubtedly true, but such cases must be heavily outnumbered by those due to rheumatoid arthritis. Compound palmar ganglion occurring in the absence of other symptoms should arouse suspicion that it may be of tuberculous origin, although there may be no other overt evidence of tuberculous infection. When the swelling behind the flexor retinaculum is large further complications such as median nerve compression may arise.

Tenosynovitis around the ankle may arise in the extensor group anteriorly, the peronei laterally, or the tibialis posterior medially. This does not appear to be such a common site as the wrist, but in any pains arising in this region of the ankle that are non-articular in origin the tendon groups should be tested individually to exclude a tenosynovitis.

Two tendon lesions commonly occur in the region of the shoulder-joint affecting the long head of biceps and the supraspinatus tendon. In bicipital tendinitis the pain is situated in the deltipectoral groove on the front of the shoulder and brought on by elevation of the arm or movements of the elbow. To make a diagnosis one has to detect pain on palpation of the tendon in the bicipital groove and pain on flexion of the elbow and supination of the forearm. This pain is aggravated by the resisted movements.

The pain in supraspinatus tendinitis extends downwards from the point of the shoulder to the insertion of the deltoid and sometimes upwards to the supraspinous fossa and trapezius; more rarely it extends down the arm to the hand. Examination of the shoulder-joint reveals little or no limitation of internal or external rotation but a painful arc on abduction. The cardinal sign of a supraspinatus tendinitis in addition to the painful arc is pain on resisted abduction of the shoulder.

Tennis elbow is not strictly a tendinous lesion but one of the tenoperiosteal origin of the common extensor muscles from the external epicondyle and supracondylar ridge of the

humerus. The triad of signs characteristic of this lesion are pain over the external epicondyle on palpation, pain on gripping, and pain at the extensor origin on resisted extension of the wrist. In this respect it has the characteristics of a tendon lesion. Reverse tennis elbow or golfer's elbow has similar signs confined to the medial epicondyle and flexor origin.

(4) *Perineural Lesions*

The fourth category of Slocumb's classification is perineural and into this fall all pains of nerve origin.

Recent developments in electrodiagnosis have permitted the conduction times in peripheral nerves to be recorded and the speed of conduction determined. Simpson (1956) has shown that in cases of median nerve compression in the carpal tunnel there is a delay in conduction in the nerve as it passes the obstruction. This enables objective evidence in favour of nerve compression to be produced when the clinical picture of paræsthesiæ with absence of objective sensory or motor loss may be equivocal, and other electrodiagnostic signs negative. In more established cases the thenar muscles, especially the abductor pollicis brevis, show wasting and at this time there will be electrodiagnostic evidence of denervation, namely, change in the intensity duration curves and on electromyography spontaneous fibrillation with a reduced interference pattern on volition.

Pain in the hand is occasionally due to lesions of the ulnar nerve either at the wrist or the elbow. A ganglion arising from the joints of the carpus can cause aching in the hand which sooner or later gives rise to wasting of ulnar distribution.

The root pains from disc lesions sometimes have a less well-recognized pattern, and hence aching down the vertebral border of the scapula, deep in the muscles of the forearm, or in the palm extending to the middle finger may be due to a prolapsed cervical intervertebral disc with pressure on the seventh cervical root. In the absence of pain in the neck this may be misinterpreted unless the neck is examined when limitation of movement or with reproduction of the pain on movement will be observed. Similarly in the lower limb sciatic pain due to a disc lesion does occasionally present as a pain in the thigh, calf or ankle without a complaint of backache. Examination of the lumbar spine, however, in these cases reveals limitation of movement, and there is usually also limitation of straight leg raising.

Root pains due to primary or secondary neoplastic involvement do not differ in their distribution from those due to more benign causes, but their intensity, continuity, and failure to respond to treatment frequently differentiate them.

(5) *Bursal Lesions*

Lesions of bursæ may be painful and they have the common diagnostic feature of giving rise to pain when compressed. There are innumerable bursæ described by the anatomists any of which may be the seat of pain, and the following three are good examples.

At the shoulder the subdeltoid bursa covers the supraspinatus tendon and in the position of abduction is squeezed. As a result there is inability to abduct beyond a certain point. This is the case when the bursa is large or acutely inflamed. In the early stages there is a painful arc on abduction and again during the stage of resolution. The onset when acute is most dramatic, abduction both active and passive being exceedingly painful beyond a certain point. This serves to differentiate from a supraspinatus tendinitis in which passive abduction which does not require the tendon to move is usually painless. Similarly there is no increased pain on resisted abduction in subdeltoid bursitis. In neither of these conditions is there any appreciable limitation of external or internal rotation of the shoulder. The subdeltoid bursa may show calcification in its walls.

Sometimes a patient presents with pain in the buttock and walks with a limp—the picture suggests a lesion of the hip or sciatica due to a prolapsed lumbar intervertebral disc. Examination fails to confirm either of these diagnoses. The pain is in the buttock, usually behind the greater trochanter, and is aggravated by three movements: full passive flexion, adduction and internal rotation of the hip-joint. There is tenderness on palpation behind the trochanter. This is the clinical picture of gluteal bursitis and this bursa may also show calcification in its walls.

The tendo achillis bursa is situated between the tendon and the posterior aspect of the tibia. When inflamed it is painful on pinching between the finger and thumb and on forced passive plantar flexion. Active plantar flexion, however, namely standing on the toes, is painless, pain on this movement being due to a lesion of the tendon itself. There is usually some palpable thickening in the post-malleolar fossa.

(6) *Panniculitis*

The panniculitis syndrome has been well described by Baker (1951), and consists of painful subcutaneous fatty deposits especially on the inner aspects of the knees, thighs and arms, and is more common in women. Because the skin does not move appreciably on more-

ment of a limb this condition does not cause pain on movement but is painful on pressure or to the touch.

(7) *Bone Lesions*

Bones themselves may be a source of pain and this pain is frequently boring in type and present both on rest and on movement. Infections such as osteomyelitis, or neoplasms such as bone tumours or myeloma have characteristic radiological appearances. Of the tissues discussed so far the bones are the first that can always be seen on X-ray and which may present the diagnosis immediately. One is accustomed to seeing Paget's disease and the skeletal rarefaction associated with osteoporosis and osteomalacia, or more rarely the cystic changes of osteitis fibrosa cystica.

## Treatment

The advent in recent years of the steroid drugs in a form suitable for local injection has found its greatest application in the soft tissue lesions of non-articular rheumatism. They have brought with them, however, the need for greater accuracy in anatomical diagnosis if they are to produce their best results. It is useless to inject the second dorsal sheath at the wrist for a tenosynovitis of the first sheath. In the past many of these conditions were treated either by heat in some form, which was applied over a relatively large field, or by massage or frictions to the tender area. These methods are still used and are effective, but probably more effective is the injection of steroid provided that it is accurately placed.

The first of the steroids available for local injection was hydrocortisone acetate prepared as a suspension, this has now been widely used for three or four years and none of the newer chemical analogues has yet been proven superior. It was thought that by esterification and the production of hydrocortisone tertiary butyl acetate the action would be prolonged but in practice there is no convincing evidence that this is so. With the advent of prednisone (delta 1: cortisone) and prednisolone (delta 1: hydrocortisone) we have had an opportunity to experiment with prednisolone trimethyl actetate. In a small number of cases in which it has been used personally on soft tissue lesions it has failed to prove its superiority over hydrocortisone acetate. In non-articular lesions duration of effect does not appear as important as in articular lesions, as in the former one injection frequently cures and the assessment of comparative duration is impossible.

## Summary

Many non-articular lesions giving rise to pain were in the past loosely classed as "fibrositis", a concept which is now believed to be incorrect. This paper stresses the accurate diagnosis of non-articular lesions based on anatomical localization in conjunction with the characteristic symptoms and signs of the individual structures involved. This diagnostic accuracy is of increasing importance following the advent of steroid drugs in a form suitable for local injection.

## References

Baker, D. (1951) *Lancet*, ii, 753.
Buschke, A. (1900) *Arch. Derm. Syph., Berl.*, **53**, 383.
Copeman, W. S. C. (1949) *Brit. med. J.*, ii, 191.
Gowers, W. R. (1904) *Brit. med. J.*, i, 117.
Simpson, J. A. (1956) *J. Neurol. Psychiat.*, **19**, 275.
Slocumb, C. H. (1943) *Clinics*, **2**, 169.
Steinbrocker, O. (1947) *Amer. J. Med.*, **3**, 402.
Stockman, R. (1920) Rheumatism and Arthritis. Edinburgh.

**Dr Hugh Burt** (London):

*Non-articular Lesions in Rheumatoid Arthritis*

In rheumatoid arthritis non-articular lesions are important, for they occur frequently, they may give rise to severe pain and disability, and they are on the whole amenable to treatment. In the past these lesions seem to have been largely unnoticed or disregarded, and even now little reference is made to them in the current textbooks. In my survey of these non-articular lesions in rheumatoid arthritis I will discuss, firstly, the foot and ankle, secondly the hand and wrist, and lastly the neck and trunk.

## Foot and Ankle

*Metatarsalgia*

Patients with rheumatoid arthritis commonly suffer from severe pain in the forefoot which is extra-articular in origin. This pain arises in the region of the metatarsal heads and sometimes radiates along the sides of the adjoining toes. In such cases a localized area of exquisite tenderness can be found on the plantar aspect when pressure is exerted

between the metatarsal heads. Most often it is the space between the second and third metatarsal heads which gives rise to pain, but other spaces may be involved either singly or in combination. Though involvement of the metatarsophalangeal joints is common in rheumatoid arthritis, I believe that the lesion I have just described is secondarily rather than primarily due to the arthritis. My reason for this belief is that its response to treatment is similar to that of metatarsalgia in non-arthritic subjects.

Some benefit may follow the application of a metatarsal bar or a well-designed insole. The treatment of choice, however, is the injection of the tender area with an anæsthetic agent. The injection should be made from the dorsal surface of the foot just proximal to the metatarsal heads, the needle being pushed between the heads until the tender area is reached on the plantar aspect. In my experience an injection of procaine produces almost immediate and lasting relief of pain, and though it is now fashionable to use hydrocortisone as well, I doubt whether the results are any better than, or even as good as, when a local anæsthetic alone is used.

*Foot Strain*

Another common finding in rheumatoid arthritis is pain arising from the proximal and middle parts of the foot. This is due to foot strain, a condition characterized by pain and sometimes swelling in the mid-part of the foot which is intensified by movements of the mid-tarsal and subtaloid joints and which is sooner or later accompanied by limitation of movement of these joints. Unlike other types of pain in the foot this pain is often not relieved by rest and may actually be aggravated by it. Foot strain is an important factor in certain types of painful feet and is likely to occur when there is any interference with normal foot mobility. A supple foot, according to Wiles (1955) "whatever the habitual posture, seldom causes serious trouble, but a stiff foot, whether it is stiff because of an unresolved sprain, arthritis or contraction of the ligaments, is liable to become painful when subjected to strain".

In the milder cases contrast baths and foot exercises may produce improvement. In cases of any severity, however, the only reliable treatment is manipulation of the foot. This can sometimes be carried out without an anæsthetic; often, however, an anæsthetic is necessary as considerable force may have to be used by the manipulator. Many would hesitate to manipulate the foot of a patient with rheumatoid arthritis, but I am convinced that such caution is unjustified provided there is no osteoporosis.

I do not regard foot strain in patients with rheumatoid arthritis as a manifestation of the arthritis itself. Its pathology is the same as that of the foot strain which follows trauma or over-use, and of that which is liable to occur after a debilitating illness. The satisfactory response of foot strain in rheumatoid arthritis to manipulation again suggests that we are not dealing with a primarily rheumatic condition.

*The Painful Heel*

The association between pain on the under aspect of the heel and arthritis elsewhere has been known for many years, and was at one time believed to be diagnostic of a gonococcal infection. We now know this to be untrue just as we have now changed most of our views concerning gonococcal arthritis. The present situation is summed up by Short *et al.* (1957) as follows: "Experience gathered chiefly in World War II has clearly established that chronic progressive arthritis, resembling rheumatoid arthritis in clinical features and course, may be precipitated or aggravated by gonorrhœal infection but in no sense represents a form of chronic joint disease due to the gonococcus."

Kahlmeter (1933) seems to have been the first to realize not only that the painful heel was common in all forms of arthritis but also that it frequently preceded the onset of arthritis. Indeed he recommended that any patient with a painful heel should have an erythrocyte sedimentation rate and other blood investigations carried out as a routine. Since Kahlmeter other observers, among them Bywaters (1954), have noted painful heels to occur in rheumatoid arthritis. More recently it has come to be recognized that a painful heel may also accompany ankylosing spondylitis, and may indeed precede symptoms in the back. Such an association was first reported by Davis and Blair (1950). Therefore in all young men with heel symptoms the sacro-iliac joints should be radiographed and the E.S.R. estimated.

Kahlmeter believed that radiotherapy was the treatment of choice of this condition and most workers would agree that the painful heels of spondylitics clear up with this treatment. Good results are also often obtained with injection of hydrocortisone into the tender spot. Accessory methods of treatment include the wearing of a sponge rubber insole.

*Achilles Tendinitis and Sub-achilles Bursitis*

Lesions in the back of the heel occur in both rheumatoid arthritis and ankylosing spondylitis. Two structures may be affected: (1) the tendo achillis, and (2) the bursa

which lies between the tendon and the posterior surface of the calcaneus. Sub-achilles bursitis occurring in rheumatoid arthritis was described by Bywaters (1954) who found it to occur in 2% to 3% of patients. He found, moreover, that if the condition persisted erosion of the underlying bone occurred. Excellent illustrations of this phenomenon can be found in Bywaters' article. When pain is acute or much swelling is present the condition is easily recognizable. Often, however, symptoms and signs are not obvious and achilles tendinitis may easily be missed in a patient with rheumatoid arthritis with involvement of the ankle when it is assumed that it is the joint which is giving rise to all symptoms in this region. I have seen at least 3 patients who must have had achilles tendinitis for years in whom the condition had been missed and whose symptoms immediately cleared up following treatment of the tendon.

As with the majority of tendon lesions elsewhere, the introduction of hydrocortisone treatment by injection has greatly altered the progress and prognosis in this type of lesion. This is an additional reason why all patients with pain in the region of the ankle should be carefully re-examined in case a tendon lesion has been missed.

## Hand and Wrist

### *Tendon Lesions in the Hand*

The occurrence of tendon lesions in arthritis was described as long ago as 1827 by Scudamore, and Stockman (1904) used the term "rheumatic tendinitis". No further reference to such a combination seems to have been made until 1924, when Helweg of Copenhagen noted the frequency with which trigger fingers occurred in rheumatoid arthritis. Helweg's papers were followed by two others also by Scandinavian physicians, namely, Kahlmeter in 1933 and Edström in 1945. In this country the first full account of the clinical and pathological findings was given by Kellgren and Ball (1950), and more recently Brewerton (1957) has discussed the condition in some detail. Study of these papers makes it clear that tendon lesions will be found in a large proportion of cases if careful examination of the hands is carried out. So far as involvement of the flexor tendons is concerned there is notable consistency in the figures of Edström, Kellgren and Brewerton, the incidence being in the region of 35%. As regards extensor tendon involvement Brewerton's figures are considerably higher than those of the other two authors. If we sum up the findings of both flexor and extensor tendon involvement reported by these authors, Kellgren found them in 37 out of 100 patients; Edström in 163 out of 391 (41·7%), and Brewerton in 193 out of 300 (64%).

The more important lesions are those in the flexor tendons; they occur commonly in the tendons of the flexor sublimis either just above or below the metacarpophalangeal joints. Kellgren and Ball described three transverse bands which cross the tendons: (1) over the middle of the metacarpal bone, (2) over the metacarpophalangeal joint, and (3) over the middle part of the proximal phalanx. They found tendinous swellings to be present in the gaps between the bands. If these swellings were large the tendon was unable to move in the sheath and flexion was interfered with. When, however, the tendon involvement was less extensive, triggering of the finger was the presenting symptom. Brewerton found triggering in 101 cases and loss of active finger flexion in 28 cases. Both Kellgren and Brewerton state that the duration of symptoms from tendon lesions is usually not more than six months though it may be as long as thirty years (Brewerton). Kellgren points out that relief of symptoms may follow stretching or breaking down as a result of the inflammatory process of the fibrous bands to which I have just referred. It is perhaps the tendency for symptoms due to tendon lesions to clear up spontaneously that accounts for their being disregarded in the literature. I suspect, however, that lack of observation is a more correct reason.

Kahlmeter obtained excellent results from radiotherapy. Satisfactory results have also been reported to follow surgery. The whole situation as regards treatment has, however, been completely changed since the introduction of hydrocortisone which in a great majority of cases produces rapid and long-lasting relief. It is for this reason that tendon lesions should always be sought, even in the presence of underlying joint disease which may become relatively asymptomatic if the tendon lesion is treated.

### *Carpal Tunnel Syndrome*

The carpal tunnel syndrome needs only brief reference. Its characteristic symptoms of pain and "pins and needles", which wake the patient up at night, are found from time to time in cases of rheumatoid arthritis. It is my experience that these symptoms are readily controlled with a light cock-up splint worn at night. It is only very seldom that hydrocortisone need be injected, and I have not yet seen a case which required surgery.

### Neck and Trunk

Many patients with rheumatoid arthritis complain of pain in the neck and trunk which in the majority of cases is non-articular in origin. Pain is usually aching in character and is likely to develop when the patient is tired or undergoing stress. Some of the pain may arise from lesions in muscles which have been described by Gibson *et al.* (1946) and by several other authors. A more important cause, however, and one which may respond to treatment, is faulty posture, or as it is now sometimes called defective postural homœostasis. The term "postural homœostasis" was first used by Barlow (1952) who rightly disliked the use of the word "posture" by itself as it implied something static whereas in fact man is constantly changing his position not only during movement but also in response to mental stimuli. Barlow's thesis is an attractive one and it is also in keeping with modern biological thought which regards man and mammal as homœostatic machines (Young, 1957).

Pain of postural origin is the result of muscular over-use or of ordinary use in muscles unequipped to withstand the stress and strain of normal existence. Sometimes in addition, there is a second type of pain which is more constant and more severe. This arises from the insertion of muscles into bone and is particularly common at the insertion of the neck muscles into the occiput. A lesion in this situation may give rise to pain which is referred to the head, and results in a constant headache which may monopolize the patient's life. A lesion here is probably analogous to that of a tennis elbow; that is to say, it is situated at the insertion of muscle into bone, it is produced as a result of prolonged contraction or tension, and is aggravated by movements which contract the muscle.

Treatment of these cases is by re-education, a necessary requirement for successful therapy being an up-to-date knowledge on the part of the therapist of the physiology of posture and, in particular, of the role of the muscle spindle. In this last connexion the work of Hunt and Kuffler (1951) is of great importance since it suggests "that the muscle spindle mechanism, which mediates much of our postural sense, is put out of action by excessive muscular contraction" (Barlow, 1956). Thus in postural re-education the present-day emphasis on muscular relaxation is physiologically right, and the traditional method of concentrating on muscle strengthening and static holding exercises is physiologically wrong.

As a substitute for postural re-education any other form of physiotherapy is not justified. As an adjunct, however, particularly in the early stages, physiotherapy is sometimes of use. Heat, massage and certain manipulations, particularly traction, all may have a place as ancillary forms of treatment.

### Summary

(1) Non-articular lesions commonly occur in rheumatoid arthritis. They may give rise to pain and disability, and materially increase the discomfort of the patient. Examples of these lesions include: metatarsalgia, foot strain, the painful heel, achilles tendinitis and sub-achilles bursitis, tendinitis of the fingers and wrists, and the carpal tunnel syndrome.

(2) Most of these lesions respond satisfactorily to treatment, the prognosis having improved greatly since the introduction of hydrocortisone by injection.

(3) Pain in the neck and trunk occurring in subjects with rheumatoid arthritis is frequently non-articular in origin; it is often the consequence of faulty posture, in which case improvement follows postural re-education.

(4) Since the non-articular lesions of rheumatoid arthritis respond well to treatment they should be sought carefully in all patients with this malady and treated, no matter how severe the joint involvement.

### References

Barlow, W. (1952) *Ann. phys. Med.*, **1**, 77.
—— (1956) *Proc. R. Soc. Med.*, **49**, 670.
Brewerton, D. A. (1957) *Ann. Rheum. Dis.*, **16**, 183.
Bywaters, E. G. L. (1954) *Ann. Rheum. Dis.*, **13**, 42.
Davis, J. B., and Blair, H. C. (1950) *J. Bone Jt. Surg.*, **32A**, 838.
Edström, G. (1945) *Nord. Med.*, **25**, 379.
Gibson, H. J., Kersley, G. D., and Desmarais, M. H. L. (1946) *Ann. Rheum. Dis.*, **5**, 131.
Helweg, C. (1924) *Klin. Wschr.*, **52**, 2383; quoted by Kellgren and Ball (1950).
Hunt, C. C., and Kuffler, S. W. (1951) *J. Physiol.*, **113**, 283.
Kahlmeter, G. (1933) *Lancet*, i, 1338.
Kellgren, J. H., and Ball, J. (1950) *Ann. Rheum. Dis.*, **9**, 48.
Scudamore, C. (1827) Quoted by Kellgren and Ball (1950).
Short, C. L., Bauer, W., and Reynolds, W. E. (1957) Rheumatoid Arthritis. Cambridge, Ma
Stockman, R. (1904) Quoted by Kellgren and Ball (1950).
Wiles, P. (1955) The Essentials of Orthopædics. 2nd edit. London.
Young, J. Z. (1957) The Life of Mammals. Oxford.

# Section of Epidemiology and Preventive Medicine

President—IAN TAYLOR, M.D., M.R.C.P., D.P.H.

[*January* 17, 1958]

## SYMPOSIUM ON WEATHER AND DISEASE

**Mr. R. G. Veryard** (Meteorological Office, Harrow):

*Availability and Processing of Meteorological Data*

There can be no disputing the fact that there is some kind of interrelationship, either direct or indirect, between many diseases to which man is susceptible and his geophysical and geochemical environment. The London "smog" disaster of December 1952 is a sad example. Yet in spite of the advances which have been made in medical and meteorological knowledge precise information is still lacking.

Now we all know that a little knowledge can be a dangerous thing, and this is particularly true of the science of Meteorology. I should therefore like to urge very strongly that the study of the relationship between weather and disease should be a joint effort on the part of experts in the various disciplines, meteorology, biology, physiology, &c.; the experts should work together as a team rather than as individuals. As an example, I can point to the joint efforts of the meteorologists and plant pathologists in the study of plant disease—efforts which have resulted in the issue, with a high degree of accuracy, of warnings of the outbreak of potato blight.

For the study of the relationship between weather and disease what meteorological data are available and how best can these data be used? First, I should mention that in this country, as in most other countries, meteorological observations are made mainly to meet forecasting requirements. By international agreement, surface observations are made at standard hours, 0, 3, 6, 9, &c. G.M.T. from a network of stations about 75–100 miles apart and upper air observations at the standard hours, 3, 9, 15 and 21 G.M.T. from a more open network of stations, about 150–200 miles apart. At many official stations, especially at airfields, additional surface observations are made every hour. To facilitate the processing of data by machine methods special forms have been devised for tabulating observations so that the information can be punched directly from the forms on to Hollerith cards. Now it is important for climatological purposes that observations be obtained from a much closer network than is needed for forecasting purposes—from a network that will include stations representative of the climatic characteristics of all types of terrain. To achieve this, the Meteorological Office has recruited about 500 co-operating stations—stations maintained by local authorities, research institutions, schools, colleges, and quite a few by private individuals. Most of these stations make observations once a day, at 9 G.M.T., and send in returns to the Meteorological Office at the end of each month. Then there are stations which provide autographic records—records of rainfall, of wind, of sunshine—as well as of temperature and pressure. Finally, there are a small number of stations which make observations of solar radiation—the direct beam, the diffuse radiation on a horizontal surface and the total radiation on a horizontal surface. A few stations record illumination and at Kew Observatory the net flux of radiation is observed. No routine observations are made of ultraviolet or of infra-red radiation: from the medical point of view this may be a pity as the ultraviolet in particular, and maybe the infra-red also, are believed to have an important bearing on human health.

In the archives of the Meteorological Office there is now a wealth of data available for research purposes. But it must be remembered that for many investigations, e.g. for the study of insect life, standard meteorological observations are of little use and it is necessary to make special observations with special instruments; the Meteorological Office has already carried out many micro-meteorological studies and can thus give useful advice regarding instrumentation for such work. It should also be borne in mind that it is misleading to think of climate in terms of averages. When considering questions of health and fitness, especially in a country which experiences such variable weather conditions as ours, extremes are important—especially extremes of radiation, temperature and humidity; but probably the greatest factor of all is the frequency and degree of the changes from day to day. There seems to be little doubt that most people react to changes of weather but it is still not known why, other things being equal, we should feel better in some weather conditions than in others. Maybe it is the cooling power of the atmosphere, maybe it is the ozone content, maybe it is the electrical state acting through the nervous system, or through

changes in the blood stream; but to determine what the factors really are careful scientific research is necessary.

Broadly speaking, there are three ways of carrying out bioclimatological and biometeorological studies—but it may be necessary to combine one method with another, or to use all three methods. The first is the purely statistical approach—the method of correlation, either to test some preconceived physical relationship, or to obtain some clue to a physical relationship. There has been an enormous amount of statistical work in the field of bioclimatology and biometeorology and, if I may say so, a large amount of this work has been quite fruitless—either because of misuse of statistics or misuse of data. For example, there is the misuse of long period meteorological records either because the data are not strictly homogeneous on account of changes in the "exposure" of the observing station (e.g. urbanization at Kew) or of climatic fluctuations, or because of the effect of "persistence". Moreover, meteorological factors do not operate as simple variables; each of several factors may influence animal response in a multi-variable manner.

A second method of investigation, which is common in meteorological and other physical sciences, is the dynamical or "energy balance" approach. A good example of this method, as applied to the field of biology, is a recent paper by Mr. C. H. B. Priestley, a meteorologist (1957). He shows how the heat balance of a sheep or other animal may be studied within the framework of a simple equation (to which Mr. E. N. Lawrence will refer later). The analysis carried out by Priestley largely separates the external or physical heat factors from the internal or physiological heat factors and thus facilitates the collation of experimental results and eases the burden on the field investigator.

This leads to the third line of attack on bioclimatological problems—the experimental approach, either in the laboratory or in "the field". A very good example of this is the work being carried out by physiologists attached to expeditions now in Antarctica who are studying the degree of acclimatization which man can acquire when he moves into a Polar region. The latter investigation has been described by Dr. Otto Edholm (1957).

One of the most neglected chapters in British climatology is the study of the health values of our climate. Fig. 1 (reproduced by kind permission of English Universities Press Ltd.,




FIG. 1.—"Bracing" and "Relaxing" climates.

from "The English Climate" by Dr. C. E. P. Brooks, 1954) shows what are called the "bracing" and "relaxing" areas of England and Wales and is based on the assessments obtained by a medical expert, Dr. E. Hawkins (1923). Maybe a meteorologist would have produced a similar map based on cooling power—I don't know. Anyway, I am sure a medico and a meteorologist working together would have produced a more reliable map!

REFERENCES

BROOKS, C. E. P. (1954) The English Climate. London.
EGHOLM, O. (1957) *New Scientist*, **22**, 26.
HAWKINS, E. (1923) Medical Climatology of England and Wales. London.
PRIESTLEY, C. H. B. (1957) *Aust. J. agric. Res.*, **8**, 271.

**Mr. E. N. Lawrence** (Meteorological Office, Harrow):

*The Application of Meteorological Data to Medical Problems*

The problems here discussed arose mainly from enquiries received by the Climatological Services Division of the Meteorological Office. They are dealt with by meteorological or medical personnel or jointly.

Mr. Veryard has emphasized that "standard" meteorological observations cannot readily be used for micro-climatological study. Their limitations are well appreciated when trying to answer the common lay question "where to live?"—perhaps in connexion with some specific disease and stating interests or requirements such as low incidence of fog, low humidity or mild temperatures. This question can be answered broadly by describing regional climates, but the effects of local or micro-topography should not be ignored. A mere pimple of a hill, 100 feet high in an otherwise plain area, may experience significantly different minimum temperatures, wind regime and ground conditions. In an industrial area, an elevated site may receive considerably more sunshine; in hilly areas, sites sheltered from wind may experience more valley fogs, mist and frost. I have found a gradient of several degrees Fahrenheit per 100 feet of height in the temperatures at one to four feet above the ground around Elstree Hill—and similar gradients elsewhere in the country. To summarize, one should realize that micro-climatic or local differences can be just as important as regional differences.

Site selection concerns not only those seeking a healthy retreat but also local councils and the Ministry of Housing when planning satellite towns. Site selection and architectural and engineering design must allow for infrequent meteorological phenomena such as strong winds, tornadoes, tidal waves and floods, and the more general conditions upon which health depends, as, for example, the limits of wet and dry bulb temperatures, the requirements for treating certain diseases and, in some regions, the climates of insect-breeding areas (e.g. rain-made breeding pools for mosquitoes) and wind direction relative to insect habitats. Health depends also on sensory comfort, and psychological or æsthetic factors.

*Thermal* comfort conditions are illustrated by data from Kip and Courtice (1945) for the East Indies. The data show that slight air movement produces a marked shift of the comfort zone towards higher temperatures. Referring to *visual* comfort, one must distinguish between hot dry climates with glare from bright ground and sunlit buildings, and hot humid climates where discomfort is caused mainly by bright sky glare. *Olfactory* comfort and air pollution are closely related to wind direction and atmospheric stability. Regarding *acoustical* comfort, wind greatly influences noise dispersion. The speed of sound equals a constant times the square root of the absolute temperature plus the "following wind" component. Sound waves tend to be refracted downwards when wind increases with height and therefore also when temperature increases with height. Thus prevailing wind direction during temperature inversion may be considerably important in avoiding noise.

An interesting investigation by the Australian Meteorological Service, in connexion with the Olympic Games held at Melbourne during November and December 1956, compared the most likely weather conditions at Melbourne during those months with conditions at previous Olympic Games and conjectured whether athletic performance would be more or less favoured than hitherto. The full investigation is described in a paper called "Weather and the Olympic Games" (published by the Bureau of Meteorology of the Commonwealth of Australia) against the background of the heat balance equation:

$$M + S + H = E + R + C$$

where M stands for metabolism, S for storage, H for short-wave radiative gain and E, R and C the evaporative, long-wave radiative and convective losses.

In the equation, M, S, E and H may be measured and from this R + C may be calculated. The possible values of the heat balance terms are quoted in the paper. Unfortunately, the experimental work obtaining the results was enacted indoors under controlled conditions and with a very low rate of air movement, 0·2 mile an hour, and the factor representing air movement is open to doubt, as no work has been carried out (at least until recently) beyond an air speed of 6 m.p.h.

Below are some examples of work done by the British Climatological Services Division: Following the London smog disaster of December 1952 detailed information on air temperature, vapour pressure and the number of hours of "thick" and "dense" fog (over

a period of eight years) was supplied to the Statistical Unit of the Medical Research Council for use in investigations on atmospheric pollution.

Study of weather conditions during certain periods of noticeable damage to laundry supplemented chemical with meteorological evidence in an investigation to ascertain the source or sources of atmospheric pollution.

A further enquiry came from a research worker desiring to relate humidity to respiratory disease. The evaporation rate inside the respiratory apparatus may be estimated from the difference between inhaled and exhaled air. Let ingoing air have an absolute temperature T, a vapour pressure of e millibars and a volume V cubic metres per hour and exhaled air a temperature of 95° F. (308° A.), a relative humidity of 95%, and hence a vapour pressure of 53·5 millibars, and a volume of 308 V/T cubic metres per hour. The inhaled air will contain 216·7 e/T grams of water vapour per cubic metre or 216·7 eV/T grams per hour and the exhaled air will have $\frac{216{\cdot}7 \times 53{\cdot}5}{308} \times \frac{308\ V}{T}$ grams per hour and the difference between these values, i.e. 216·7 V (53·5-e)/T grams per hour represents the rate of loss of moisture. This expression indicates that the relevant "humidity" element is vapour pressure. In January, moisture loss is 25% greater than on an average day in July. On the coldest winter day, evaporation may be from 50 to 75% greater than on a sultry day in summer.

A further avenue of investigation concerns poliomyelitis. Briefly, much attention has been given to temperature and humidity (or some measure of atmospheric moisture content). The writer has computed (Lawrence, 1956) the correlations of maximum weekly notifications and total annual notifications with annual "accumulated degree-weeks" (computed from the weekly mean temperature in England and Wales) from a base of 60° F., and obtained values of 0·85 and 0·83 respectively, which are indeed rather striking. These results do not preclude a close relationship between poliomyelitis and some measure of evaporation or atmospheric "drying power", for the function of accumulated temperature employed is indicative of the atmospheric "drying power" of a particular summer in Britain.

## REFERENCES

KIP, C. J., and COURTICE, R. (1945) *Heat. Pip. Air Condit.*, **17**, 6.
LAWRENCE, E. N. (1956) *Met. Mag., Lond.*, **85**, 164.

**Dr. P. J. Lawther** (Medical Research Council Group for Research on Atmospheric Pollution, St. Bartholomew's Hospital, London):

*Climate, Air Pollution and Chronic Bronchitis*

The clinical condition of patients with chronic bronchitis may vary markedly from day to day. The influence of weather is commonly recognized and the serious effects of gross urban pollution have been manifest in various smog episodes. Recrudescence of infection is, of course, another important factor. In towns climate and air pollution are closely linked and both merit attention as possible ætiological factors in the production of chronic bronchitis as well as causes of exacerbation. It is important to recognize the separate nature of these divisions of the problem. Likewise it must be realized that the chemical and physical nature of polluted air is extremely complex and as yet ill-understood; pollution varies widely in both quality and quantity. Recent analytical work (Waller and Lawther, 1955, 1957) has shown that it is dangerous to regard smog as a specific miasma compounded of smoke and fog; it is wiser to regard fog and pollution as having more independent lives of their own, though obviously their coincidence is of chemical and clinical importance (Fig. 1).

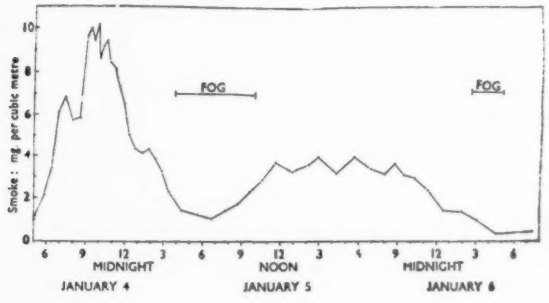



FIG. 1.—Concentration of smoke and occurrence of fog in London during a "smog" period in January 1956.

[From *Brit. med. J.* (1957) *ii*, 1473; by kind permission]

Smog is better referred to as acute urban pollution and it ought to be regarded as a rare and freakish occurrence. It is not merely a quantitative variant of the day-to-day airborne dirt. The effects of air pollution and various climatic factors may be investigated by two complementary techniques: the *experimental* approach involves the exposure of subjects to isolated factors under controlled conditions and the effects must be interpreted with due recognition of the limitations of the method. The *epidemiological* approach consists of the observation of the undisturbed patient in his carefully defined environment. Elaborate techniques are necessary only if the truth of the matter is deeply hidden, and the crude method described here illustrates the value of a simple initial approach to the problem of the separate effects of weather and pollution.

In 1954 patients who regularly attended a special clinic at St. Bartholomew's Hospital for chronic bronchitis and emphysema were given diaries in which they were asked to record their own assessment of their condition by means of a simple code

A. Condition **BETTER** than usual.
B. Condition **THE SAME** as usual.
C. Condition **WORSE** than usual.
D. Condition **MUCH WORSE** than usual.

The state of the group was plotted against pollution and climatic data and the value of this technique was quickly established when it was seen that an episode of acute pollution in the absence of fog resulted in marked clinical deterioration of the patients (Fig. 2).

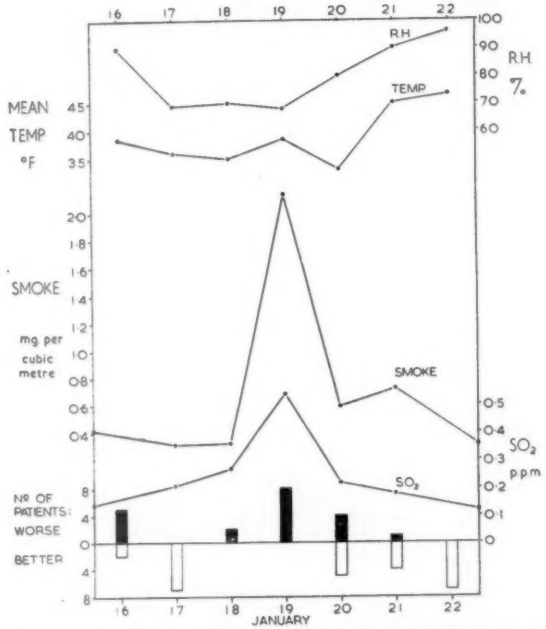



FIG. 2.—Graph showing effect on 29 bronchitic patients (St. Bartholomew's Hospital) of high pollution without fog.

[From *Brit. med. J.* (1955) *ii*, 1356; by kind permission]

A method of scoring was applied to subsequent results, from which was derived a figure called the "degree of illness":

$$A = -1;\ B = 0;\ C = 1;\ D = 2.$$

$$\text{hen Mean Score} = \frac{\text{Sum of scores for all patients}}{\text{Number of patients}}$$

he mean score provides a measure of the "degree of illness" of the group as a whole, inging from 0 to 1 in winter and falling below 0 in summer.

In the winter of 1955 the scheme was extended (with the kind help of Dr. C. M. Fletcher and other chest physicians) to five centres in London and others in the provinces. It was hoped that in the event of a smog disaster it would be possible to correlate the diary results with special tests made by the Department of Scientific and Industrial Research. These tests proved to be of limited value but the diary results yielded very valuable information. 180 diaries from patients in the London area were examined and the degree of illness of this population plotted against pollution and climatic data measured in central London (Fig. 3).

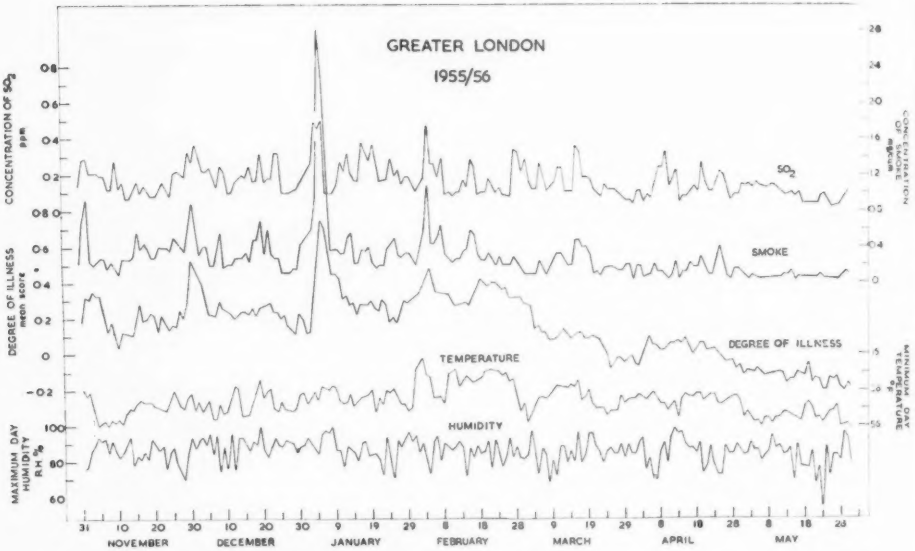



FIG. 3.—Graph showing degree of illness of a group of 180 patients in Greater London with chronic bronchitis, plotted with smoke and $SO_2$ concentrations, temperature and humidity.

[From *Instrument Practice*, 1957, **11**, 611; by kind permission

The degree of illness is seen to be more closely related to pollution than to any other factor during the winter months but this connexion disappears when pollution falls in the spring. It is noteworthy that decreases in visibility do not always correspond to a worsening of the condition of the group and this strengthens the suspicion that fog itself may play a less important part than was formerly thought. These results do not imply any direct causal relationship between smoke and $SO_2$ and the clinical state of the patients, but show that pollution, of which these substances are at least indicators, is probably causally involved. The scheme has again been extended and further analytical data, including sulphuric acid measurements, are being collected. The interpretation of these results is as yet very incomplete, but they provide for the first time evidence that chronic bronchitis is influenced markedly by day-to-day variations in urban atmospheric pollution.

## REFERENCES

LAWTHER, P. J. (1957) *Instrum. Pract.*, **11**, 611.
WALLER, R. E., and LAWTHER, P. J. (1955) *Brit. med. J.*, ii, 1356.
——, —— (1957) *Brit. med. J.*, ii, 1473.

**Dr. B. B. Waddy** (London School of Hygiene and Tropical Medicine):

*Atmospheric Humidity and Air-borne Epidemics*

The countries bordering on the south and east of the Sahara experience cerebrospinal meningitis (c.s.m.) in a way with which no other part of the world compares. For example, c.s.m. was epidemic in the United Kingdom in 1940 and 1941; adding together the figures for the two years the attack rate was roughly 1 : 10,000. Ordman (1932) gave an attack rate of 3 : 1,000 as the greatest he found in an exhaustive historical survey of the disease in southern Africa. In contrast to these figures, in a large area of Northern Nigeria the

*mortality* rate in a single season was estimated at 33 : 1,000, and in the cycle of epidemics in the western Northern Territories of Ghana with which I was concerned the total attack rate was 81·9 : 1,000. Lobar pneumonia also is an epidemic disease there.

Epidemics of this severity occur only during the dry season, and only in the dry savannah areas of the Sudan, Nigeria, Ghana and the intervening French territories. All epidemics end at the same time, the end of April. When c.s.m. is first introduced into a susceptible area the epidemic seldom gets under way until about the middle of February, half-way through the dry season. The first epidemic, therefore, is usually not a very big one. There are never more than occasional sporadic cases during the rains, but in its second dry season in an area the epidemic may start at the very beginning of the dry season—the turn of the year. With seven or eight weeks longer in which to develop, the second season's epidemic in an area tends to be the enormous one, and apparently leaves local mass immunity.

In the Northern Territories of Ghana it has been possible to trace the complete epidemiological picture of c.s.m. since its first introduction there in 1906. Apart from being confined to the dry season, intense epidemics are also confined to only the western side of the Northern Territories. The only explanation of this lies in the different types of house in common use. In the epidemic-free areas the dwelling consists of thatched round-houses each with a door opening on to a central compound; in the epidemic area the houses have mud roofs; they may be enormous in size, with perhaps 300 rooms, and most of the rooms are reached by internal connexions from very few outside opening doors. Inside them, therefore, there is a complete absence of ventilation and impenetrable darkness.

Epidemic lobar pneumonia has the same distribution and seasonal timing. Smallpox is not so strictly dependent on climate, but in the savannah smallpox epidemics invariably die out at the end of the dry season. Everything in this epidemiological picture is extremely clear-cut although no bacteriological work has been done. Glover's conception of the epidemic following in the train of an increased carrier rate would fit the observed facts of African c.s.m., if the carrier rate is dependent on dryness of the atmosphere. Initially, the carrier rate rises slowly from a small nucleus of migrant carriers, so that epidemic conditions take some weeks to ensue. At the end of the dry season carrier rate and epidemic die away rapidly and simultaneously, leaving a number of chronic carriers. These make a more widespread infective nucleus at the start of the next dry season, when the epidemic develops earlier.

In temperate climates, since the time of Hippocrates it has been known that air-borne epidemics tend to occur in late winter and after cold snaps, the change of weather taking about a month to take effect. Unless the epidemiology differs radically from that in the tropics, there must be something in common between the English home in February and the inside of a particular type of African house during the dry season. There are two such factors.

The first is a lack of daylight. Miller and Schad (1944) found that the meningococcus survived and kept its virulence for at least a week if kept dry and cool and in complete darkness, and that survival was roughly inversely proportional to the intensity and shortness of wavelength of light to which it was exposed. Field observations fit in with this finding. The evidence of the different types of house in Ghana is very striking. In England and Wales in 1940–41 there were higher attack rates in counties in which coalmining was the predominant occupation. In New Zealand, Dixon (1943) found an association with refrigerator workers. The common factor is darkness or artificial light.

The other factor is low absolute humidity (A.H.). In the epidemic zone of Africa, relative humidity (R.H.) drops extremely low during the dry season, and A.H. follows an exactly parallel course. In temperate climates A.H. is almost independent of R.H. and entirely dependent on temperature, being at its lowest in February and highest in July and August (Figs. 1 and 2). C.s.m. incidence in 1940 and 1941 showed obvious peaks at the nadir of the A.H. curve. In fact, the A.H. on a cold foggy day in England and a dry hot day in Africa are very much the same, 2 to 4 grams per cubic metre.

In Ghana in 1948 between case incidence and the A.H. of four weeks previous there was a correlation coefficient of −0·53, s.e. 0·20. In this country, the only prolonged series of carrier rates of which I know is that of Glover (1918). The correlation coefficient between carrier rate and A.H. of four weeks previous was −0·78, s.e. 0·29. The A.H. figures were outdoor ones, but experiments I made myself during the winter of 1947 showed that the indoor A.H. does not rise very much above that outdoors (Waddy, 1952).

Elsewhere in the tropics, Rogers (1926) correlated smallpox and lobar pneumonia with low A.H. The association of the three waves of the 1918–19 influenza pandemic with cold dry weather was noted both in this country and in France. More recently Thorburn (1957) correlated air-borne infections with low A.H. in southern Africa.

There is experimental evidence that air-borne organisms do live longer in conditions of low A.H. (de Ome, 1944; and Loosli *et al.*, 1943). As far as is at present known, therefore,

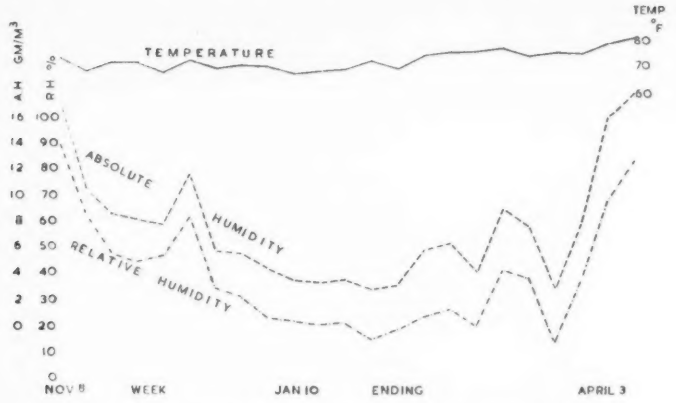



FIG. 1.—The tropical dry season. Ghana, 1947–48.

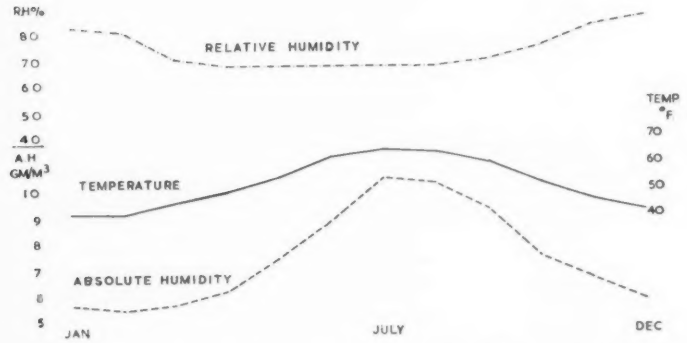



FIG. 2.—Average temperature, relative and absolute humidity in England (Harrogate).

bacteriological evidence supports field epidemiology. So does physiological evidence. The amount of water that has to be evaporated in the upper respiratory passages and added to the inspired air depends on the absolute, not relative humidity of the outside air. Looked at from this point of view, the saturated air of a February day, A.H. about 4 grams per cubic metre, is very much drier than that of a hot dry July day, A.H. about 11 grams per cubic metre. The evaporation of water produces also a cooling effect, and it is well known that ciliated epithelium does its job sluggishly when cooled. This may well apply specially when there has been a sudden change of weather, before physiological adaptation has taken place.

## REFERENCES

DE OME, K. B. (1944) *Amer. J. Hyg.*, **40,** 239.
DIXON, C. W. (1943) Annual Report, North Auckland Health District, New Zealand.
GLOVER, A. (1918) *J. Hyg., Camb.*, **17,** 350.
LOOSLI, C. G., LEMON, H. M., ROBERTSON, O. H., and APPEL, E. (1943) *Proc. Soc. exp. Biol. Med.*, **53,** 205.
MILLER, C. P., and SCHAD, D. (1944) *J. Bact.*, **47,** 71.
ORDMAN, D. (1932) *S. Afr. med. J.*, **6,** 757.
ROGERS, L. (1926) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 106.
THORBURN, W. B. (1957) *Brit. J. prev. soc. Med.*, **11,** 36.
WADDY, B. B. (1952) *Lancet*, ii, 674.

# Section of General Practice

President—G. M. KERR, M.B., L.R.C.P., F.F.A. R.C.S.

[*January* 15, 1958]

## DISCUSSION ON THE COMMON COLD

**Dr. R. E. Hope Simpson** (Cirencester):

When we have been baffled by a problem for a sufficient time, when we have assaulted it with this theory and that hypothesis and it remains unsolved to plague us both intellectually and physically, it may be that the time has come to imitate Joshua, to draw our forces a little way off, to march round and round our problem considering it from every angle. Inferences may then suddenly become so plain to us that we blow loudly on the trumpets of a new idea and down tumble the impregnable walls. Some such feeling has animated our approach to the problem of the common cold, a fortified city that has so far successfully resisted the most determined and persistent frontal attacks. I shall consider one aspect from my own vantage point.

For many years we studied the broad picture of respiratory disease as presented to us in general practice. In particular it seemed important not to assume that colds were infectious unless the facts proved them to be so and I shall quote certain features of the epidemiology of colds which are inexplicable by a theory of simple transmission.

J. J. van Loghem collected records from nearly 8,000 volunteers in various parts of Holland. He analysed them separately for seven different regions of Holland and found nearly the same incidence in each region, and that the secular curves of morbidity of each had approximately the same troughs and peaks. It is as if one started measles in seven different parts of a country simultaneously, then selected susceptible volunteers at random from the seven different regions, and when the epidemic was over one found that the measles amongst the volunteers gave identical curves of prevalence and incidence in each region. Such a thing would be an incredibly unlikely coincidence, yet this actually happened with colds and has since been confirmed by Frost and Gover and again by Tucher in the United States. Some other powerful agency must be in operation besides case-to-case transmission, if such indeed does occur.

Rarity and commonness in diseases are interesting characteristics worthy of close attention. A common disease presents the difficulty that its very abundance may make it almost impossible to decide whether case-to-case transmission occurs or not. Colds may be so abundant that the appearance of transmission is simulated by chance alone.

A second characteristic, in addition to the extreme abundance of colds, is their seasonal tide. The five-year average of cases of respiratory disease presenting in each calendar month in the practice gives a curve with its peak in the winter months and its nadir in the summer. The thirty-five-year average each month for the air temperature when inverted shows a broad parallelism with the respiratory disease curve.

This parallelism with the temperature did not hold for cases of sore throat. It seemed that a big group of respiratory illnesses, the commonest diseases with which we have to deal, followed a seasonal trend running to abundance in the cold weather, and that another symptomatically distinct respiratory group did not. This crude epidemiological observation merited a closer scrutiny. We therefore enrolled some 350 volunteers, about 80 families, who keep a daily record of certain respiratory symptoms.

*Incidence.*—We had two main objectives, firstly to discover in detail the true incidence, and secondly to see how closely colds paralleled the changes in seasonal temperature. Here again we tried to shed our preconceptions. We did not in the first place record colds, separate illnesses, as units or episodes but we recorded the daily morbidity in case colds were not episodes of illness like measles. We hoped that the facts if adequately and accurately elicited would speak for themselves. We did not know what other mode of illness there might be. Perhaps a state of chronic morbidity with the morbid process increasing in severity every now and then so that its toxicity rose above the threshold of symptom production and then again sank below it, or perhaps a latent virus infection prompted to periodic activity by extraneous agencies in the manner of herpes simplex virus, or again, perhaps the normal bacterial flora prompted to unwonted activity by the advent of viruses passing continuously from person to person. Whatever the possibilities we had no right, in view of the quite different epidemiological picture presented by colds, to carry over to this enquiry conceptions based on the epidemiology of diseases like measles and typhoid fever. If we can be sure of anything, we can be sure of this, that in colds we have to deal with a mode of illness totally different from those.

Each of us probably suffers from measles for two of the 3,500 weeks of his life. How long do we suffer from colds? Our figures for 1954 and 1955 suggest that we probably suffer from a cold for 700 weeks of our life—one-fifth of our days. During each of these years the average for man, woman and child was seven episodes of respiratory illness averaging ten days each—seventy days per annum.

Though this may be a minor disease it is not a minor mode of illness.

*Seasonal link.*—How closely are colds associated with cold?

The secular curve of morbidity from colds amongst our volunteers was compared continuously on a comparable scale with the inversion of the temperature taken a foot deep in the earth. This gives a good picture of the seasonal temperature damping out the effects of brief erratic changes in the air temperature (Fig. 1). The concordance between the two curves is remarkable. It seems that the temperature has only to drop 1° F. for the morbidity from colds to rise by about 1%.

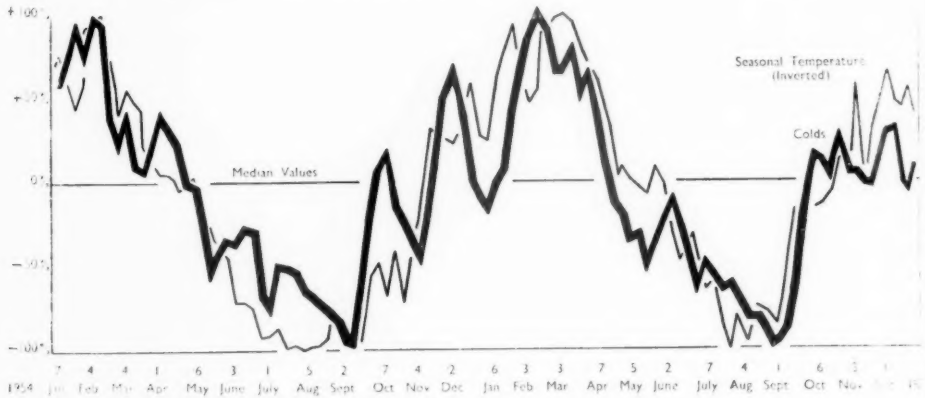



FIG. 1.—*Morbidity from colds with seasonal temperature* 1954 *and* 1955. Thick line—percentage of volunteers showing symptoms. Thin line—earth temperature (inverted).

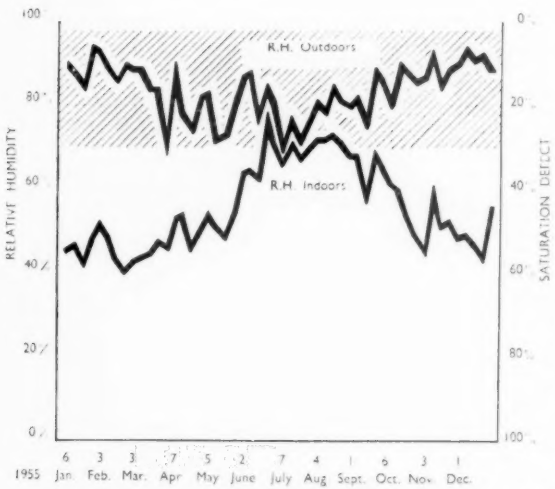



FIG. 2.—*Relative humidity outdoors and indoors* 1955. Top curve—relative humidity at 10.0 a.m. outdoors. Lower curve—relative humidity at 3.0 p.m. indoors. Shaded area shows the usual range of natural outdoor relative humidity.

It is, of course, possible that the drop in seasonal temperature itself directly causes the increased morbidity, but one finds difficulty in accepting this solution of the problem. The effect may be secondary, mediated through another agency acting directly on the human organism, an agency the effect of which varies in intensity with the seasonal temperature change. This seems the more likely because most of us spend much of our time, especially in winter, in temperatures far removed from those of the outside air, and yet it is in winter particularly that we must seek the baleful agency. In the search for this agency our suspicions were aroused by the humidity of the indoor atmosphere, or, to be more precise, by the converse of

the humidity, the evaporating power or dryness of the air. Here is an agency acting directly on the respiratory apparatus in the most intimate fashion imaginable.

Direct evaporimetry is tricky, but it is fairly easy to obtain a measure of the drying effect of the air from the saturation deficit and the temperature. The saturation deficit tells us in percentages how much more water vapour the atmosphere can accommodate, and the temperature allows us to envisage the avidity of the air for water. The usual range of humidity of the outdoor air in our part of the world is from 70% to 98% with an average of about 80%. This has a deficit of from 30% to 2%. For a brief period in summer the air indoors reaches this "natural" state of humidity (Fig. 2). For most of the year, however, the air indoors is considerably drier than the outdoor air.

The difference in humidity between the atmosphere indoors and outdoors gives a curve over the year that approximates very closely to that of the morbidity from colds, in fact we may say that the increase of colds and the increase of dryness due to artificial heating run closely parallel (Fig. 3).

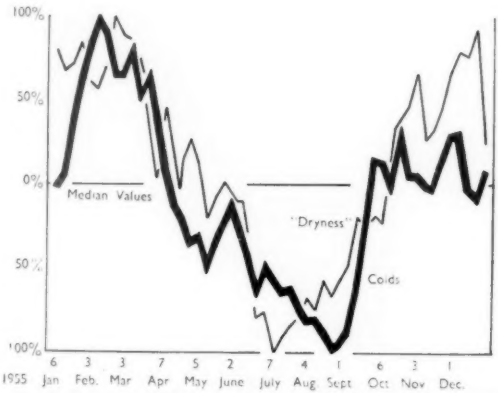



FIG. 3.—*Colds and indoor dryness* 1955. Thick line—morbidity from colds. Thin line—difference between relative humidity outdoors and indoors.

Our respiratory apparatus requires that the air shall be fully saturated with water vapour if it is not to suffer severe damage. Lassen discovered this tragically when poliomyelitis hit Denmark and produced the great crop of cases of bulbar palsy. They found themselves faced with numerous patients unable to breathe and only two iron lungs in the country. Lassen rapidly improvised methods of positive-pressure respiration with anæsthetic apparatus. He found that unless the gases were fully saturated the patients developed respiratory infections. Here is clear evidence of the importance of an adequate content of water-vapour, and we know that there is an apparatus in the human nose and upper respiratory passages for saturating incoming air. This humidifying apparatus, it is reasonable to suppose, is designed to meet the exigencies of the "natural" variations in humidity, but the conditions indoors depart widely from anything that we meet outdoors, especially in winter. Moreover, the effect is enhanced enormously by the temperature. For each 10° rise in temperature we get a

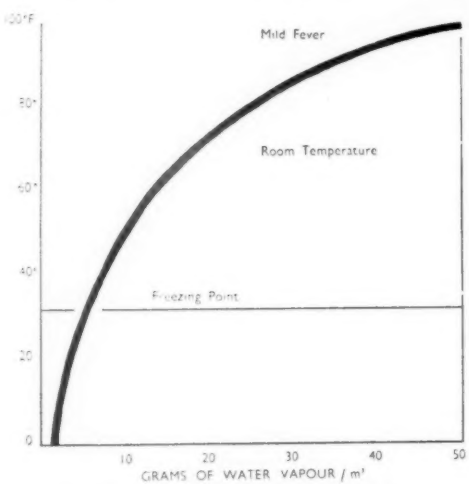



FIG. 4.—*The saturation content of the air at different temperatures.*

proportionately increasing capacity of the air to store water, coupled with an enhance molecular activity, so that the thirst of the air develops enormously as one proceeds u the scale (Fig. 4).

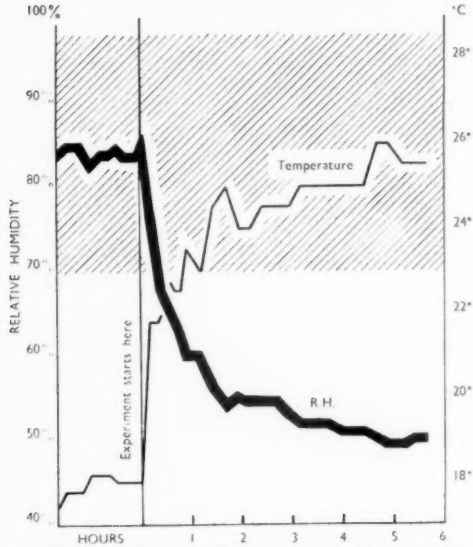



FIG. 5.—*Impotence of open door and window to keep the room moist after switching on a one-bar electric fire.* Thick line—relative humidity. Thin line—temperature. The relative humidity drops rapidly below the natural (shaded) level.

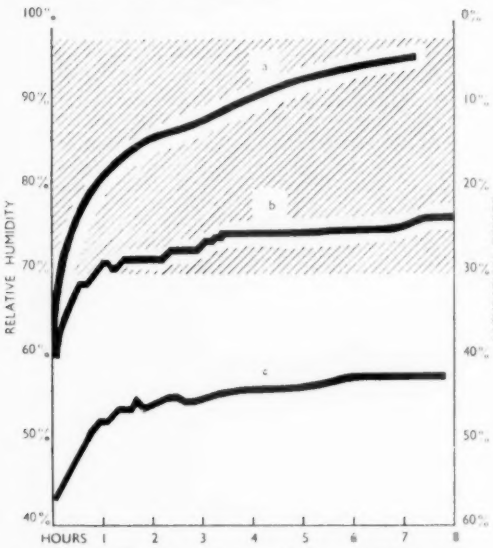



FIG. 7.—*The effect of a humidifier.* (*a*) Without any artificial heat (room temperature 20° C.). (*b*) With a single-bar electric fire (room temperature 25° C.). (*c*) With a double-bar electric fire (room temperature 30° C.). Shaded area represents "natural" relative humidity.

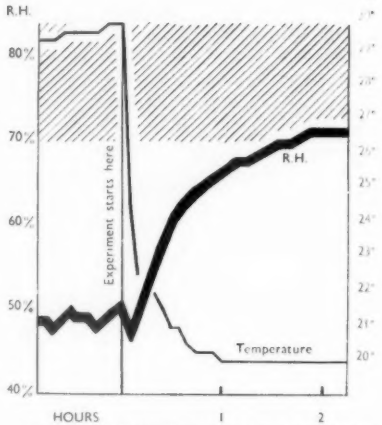



FIG. 6.—*Effect of opening door and window in a dry hot room without a source of artificial heat.* Thick line—relative humidity. Thin line—temperature. The humidity rapidly rises to a natural level (shaded area).

The bronchial tree is lined with ciliated epithelium continuously in action wafting a stream of mucus in spiral fashion towards the mouth. Upon this mucus stream fall all the particles of dust, the airborne bacteria, and viruses. They are washed upwards until they reach the mouth and are swallowed. Dry air can so thicken the mucus that it impedes the action of the underlying cilia. Over long periods of time this might lead to areas of irritation and damage to the underlying cells and certainly would impair the cleansing mechanism of the respiratory tract. Bacteria and viruses might find themselves in regions unaccustomed to their presence, locally non-immune, so that they might set up temporary inflammatory processes. Osmotic changes in the cells might also lead to trouble.

Opening the windows of the room does not put all this right. When the room is moist and cool to a degree equivalent to the outside air and the electric fire is switched on, the atmosphere rapidly becomes warm and dry and in almost no time the humidity is far below the outdoor level (Fig. 5). Switch off the fire and open the door and window and the air soon becomes moist (Fig. 6). Even with a humidifier

continuously working it is difficult to bring the air into the region of natural humidity whilst an electric fire is switched on (Fig. 7).

*Summary*.—The common cold is a mode of illness that attacks with a frequency far outstripping that of any other disease. The incidence is so closely correlated with seasonal temperature that a drop of 1° F. is associated with an increase of 1% in morbidity. We found that the drying and warming of the air by the artificial heating in our houses provided a most suggestive association with the morbidity from colds.

It is difficult to design an experiment to settle the importance of this factor, but we were fortunate enough to obtain a record which contributes to the subject. A cheese factory in Wales was recently provided with a room kept at a temperature of about 57° F. and a humidity of 80%. It was feared that the workers in this room might suffer from the high humidity and cold atmosphere. In fact over a period of twelve months their morbidity rate was less than half that of the other workers in the factory.

**Dr. A. T. Roden** (London):

*Clinical Assessment of the Common Cold*

While engaged in a study of the records of the Common Cold Research Unit at Harvard Hospital, Salisbury, I became interested in the question—What criteria does the clinical observer use in making his assessments?—and as a corollary to that—How consistently does he apply them?

The volunteers who come to this Unit live, usually in pairs, in isolation accommodation. Clinical observations are recorded daily. For my present purpose I have abstracted from the records the following signs and symptoms—nasal discharge, nasal obstruction, sore throat, cough and pyrexia.

Table I shows such an abstract from the record of an individual volunteer. The days

TABLE I.—MILD COLD

| | Days 1 | 2 | 3 | 4 ↓ 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Clear discharge .. | | | | | + | + | ± | ± |
| Purulent discharge | | | | | | + | ± | |
| Extra handkerchiefs | | | | | 9 | 30 | 15 | 1 |
| Nasal obstruction | | | | | | ± | ± | |
| Sore throat .. | | | | ± | ± | | | |
| Cough .. .. | | | | | | | | |
| Fever .. .. | | | | | | | | |

TABLE II.—MODERATE COLD

| | Days 1 | 2 | 3 | 4 ↓ 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Clear discharge .. | | | ± | | + | + | + | + |
| Purulent discharge | | | | | + | + | + | + |
| Extra handkerchiefs | 1 | 1 | | 1 | 8 | 11 | 7 | 6 |
| Nasal obstruction | | | | | | + | | ± |
| Sore throat .. | | | | | + | | | |
| Cough .. .. | | | | | | | | ± |
| Fever .. .. | | | | | | ± | | |

begin and end at noon. The first four days were a preliminary period of observation during which the volunteer was free from symptoms. At the end of the fourth day infective material—from the nasal secretions of a person suffering from a common cold—was administered by intranasal instillation. Within twenty-four hours—or to be more precise about eighteen hours—after administration the volunteer felt a slight soreness of the throat. The next day there was an increase of nasal discharge, at first clear but, by the following day, muco-purulent. At the height of the nasal discharge there was slight nasal obstruction. No cough. No pyrexia. The assessment—mild cold.

Here is an example of a minor respiratory illness of which the predominant clinical manifestation is an increase of nasal exudate. Now, in my reading of the medical literature, I have yet to come across any adequate description of the quantity of the nasal discharges either in health or in disease. I may not have carried my reading far enough. But if I am right this is a very surprising omission. Because a rough quantitative estimate can be based on quite simple observations and would, presumably, have been made by many clinicians if it were thought to have a diagnostic value.

The extra handkerchiefs used were of paper. They are called "extra" because each volunteer is allowed one as a normal daily ration. The symbol + against nasal discharge indicates that the quantity on the handkerchief was such that it could not be used again without unpleasantness. The symbol ± indicates a perceptible quantity but such that the handkerchief could have been used again.

Table II shows another individual record. Again there is the same preliminary period of observation during which there was a little insignificant nasal discharge. On the second day after administration of infective material—coryza and sore throat. At the height of the coryza, transient slight pyrexia—in this instance about 99·6° F. Later some slight cough. The assessment—moderate cold.

The assessment is interesting. The degree of coryza just exceeds the minimum amount

in category 4 of our arbitrary scale (*see* below) with 8 extra handkerchiefs on one da and 11 on the next. In Table I the volunteer with the mild cold used 9 extra handkerchief on one day and 30 on the next. So the severity of the cold has been judged not by th degree of coryza alone but by the combination with other symptoms and by the genera misery of the patient.

The following is a summary of observations on a total of 407 volunteers, of whom 19 were given positive control material—that is material from persons suffering from a col and, therefore, presumably infective—and 209 were given negative control material—tha is some inert fluid. I have not brought into this summary any volunteers given cultur materials under test for the presence of virus.

All the assessments were made by one clinical observer and all his observations o positive and negative control groups have been included. The volunteers were allocate at random to their groups and neither they nor the observer were aware of the nature of th material used until the assessments had been recorded. This is a normal experimenta precaution against bias.

In Tables III to VI the degree of coryza—using coryza as a synonym for increased nasa discharge—is represented on the following arbitrary scale:

0 = None or ± only.
1 = + on one day only.
2 = + on two days or more.
3 = + with at least 8 extra handkerchiefs on one day only.
4 = + with at least 8 extra handkerchiefs on two days or more.

Table III shows the correlation between the degree of coryza on the arbitrary scale and

TABLE III.—CORRELATION OF CORYZA WITH OTHER SYMPTOMS

| | | Other symptoms | | |
|---|---|---|---|---|
| | | − or ± | + | %+ |
| Degree of coryza | 0 | 263 | 17 | 6·1 |
| | 1 | 26 | 4 | 13·3 |
| | 2 | 25 | 20 | 44·4 |
| | 3 | 3 | 9 | 75·0 |
| | 4 | 3 | 37 | 92·5 |
| | Total | 320 | 87 | 21·4 |

the presence of one or more of the other symptoms and signs which I have mentioned. This correlation may be taken as evidence that both the coryza and the other symptoms have a common causation.

The figures from the second and third columns of Table III are set out thus: 263 in the category 0−, 17 in the category 0+ and so on, in relation to the clinical assessments.

Table IV shows our ten categories and the assessments—no cold (−), doubtful cold (±),

TABLE IV.—RELATION OF ASSESSMENTS TO SYMPTOMS

| | | Assessments | | | | | |
|---|---|---|---|---|---|---|---|
| | | − | ± | m | M | S | Total |
| Degrees of symptoms | 0− | 254 | 9 | — | — | — | 263 |
| | 0+ | 11 | 5 | 1 | — | — | 17 |
| | 1− | 20 | 5 | 1 | — | — | 26 |
| | 1+ | 1 | 3 | — | — | — | 4 |
| | 2− | 8 | 10 | 7 | — | — | 25 |
| | 2+ | — | 7 | 9 | 4 | — | 20 |
| | 3− | — | — | 3 | — | — | 3 |
| | 3+ | — | — | 6 | 3 | — | 9 |
| | 4− | — | — | 3 | — | — | 3 |
| | 4+ | — | — | 13 | 19 | 5 | 37 |
| | Total | 294 | 39 | 43 | 26 | 5 | 407 |

mild (m), moderate (M) or severe (S) cold. It will be observed that in categories 0 and 1 only 2 out of a large number reach an assessment of mild cold. In categories 3 and 4 all are assessed as colds. Between, in category 2, there lies an ambiguous zone. In each category it will be seen that the presence of other symptoms influences the assessment.

Tables V and VI show the degree of coryza and the assessments in relation to the experimental procedure.

TABLE V.—NEGATIVE CONTROLS

| | | Assessments | | | No. of cases |
|---|---|---|---|---|---|
| | | − | ± | + | |
| Degree of coryza | 0 | 176 | 7 | — | 183 |
| | 1 | 10 | 2 | — | 12 |
| | 2 | 5 | 8 | 1 | 14 |
| | 3 | — | — | — | — |
| | 4 | — | — | — | — |
| | Total | 191 | 17 | 1 | 209 |

TABLE VI.—POSITIVE CONTROLS

| | | Assessments | | | No. of cases |
|---|---|---|---|---|---|
| | | − | ± | + | |
| Degree of coryza | 0 | 89 | 7 | 1 | 97 |
| | 1 | 11 | 6 | 1 | 18 |
| | 2 | 3 | 9 | 19 | 31 |
| | 3 | — | — | 12 | 12 |
| | 4 | — | — | 40 | 40 |
| | Total | 103 | 22 | 73 | 198 |

Table V—the negative control group—shows that in no instance did the degree of coryza rise above the ambiguous zone. One volunteer out of 209 managed to achieve assessment as a mild cold.

Table VI—the positive control group—shows the degree of coryza observed and the assessments made of definite colds in 73 out of 198 volunteers.

I have used these data to illustrate two aspects of the rationale of clinical judgments.

First by an examination of the primary observations to ascertain the degree of consistency of the assessments.

Second to test the validity of the clinical concept against some factor—in this instance the nature of the experimental procedure—which is independent of the clinician's judgment.

**Dr. J. Morrison Ritchie** (Birkenhead):

In 1930, when the Birkenhead Municipal Laboratory was opened, a female clerk of the M.O.H. Department who had been a martyr to colds for years was very persistent in demanding treatment. On the understanding that she would have an injection once a week during the following winter no matter what happened, I made her an autogenous vaccine from her sputum.

She went through the winter without a cold, the first time for years. At the end of the following summer (1931) she and several others asked for a vaccine. They all had a winter without colds, although some had the prodromal stages. We then had, for years, a procession of corporation staff, much against my will, but it soon seemed that our only failures were where actual damage had occurred to mucous membrane. The theory was evolved that the function of the virus might be essentially to depress resistance, so giving the normal (though heterogeneous) nasopharyngeal flora a more or less free hand—in other words, the virus is a kind of starting handle.

When the Birkenhead Laboratory was taken over by the Public Health Laboratory Service, permission was obtained from Professor Wilson for a controlled experiment, and a series on approximately 200 volunteers was carried out during the winter of 1955–6, in conjunction with the factory at Port Sunlight. Of these, allowing for wastage, 109 were given autogenous vaccines prepared from their saliva, while 75 got saline injections only. Apart from prodromal stages, i.e. a clear running nose for a couple of days (presumed to be the virus activity which was relatively unaffected), the percentage of full colds was six times as high in the controls as among the vaccinees who were able to carry on throughout the winter. I gave the vaccines, while assessment was carried out by Port Sunlight's staff, who did not know who were controls.

This was very encouraging, but naturally autogenous vaccines on a large scale are not practicable, so the idea was tried of tackling the problem from the opposite angle, i.e. instead of boosting the patient's resistance, to depress the activity of the bacteria at the appropriate time. Without going into details, the proposal was to do a series of sensitivity tests on the saliva of volunteers and card the results, this being done before the cold season began. Then, when each reported the beginning of a cold, the works Medical Centre

would issue the appropriate antibiotic tablets. In short, the idea now was to balance the depression of the patient's resistance by a corresponding temporary depression in the activity of the bacteria. The minimal dose of four tablets spread over two days was used to avoid interference with the patient's normal flora or the production of insensitive organisms.

For this later investigation, altogether just over 1,000 volunteers were available, in half a dozen works, a large office staff, and a school, all assessment being done by the Medical Centres concerned. Inert tablets were used as controls. The Birkenhead Police also co-operated, using the Laboratory as Medical Centre, and they became a day-to-day check on the investigation, without controls, being for this reason excluded from the investigation itself. This check was very useful, as it was found that in a few cases four tablets gave a rather short course and five or six would abort the condition. Once more the clear running stage for twenty-four to forty-eight hours was regarded as prodromal, due to the virus, but it was strange how many people used the phrase "turned off like a tap" after that period.

There were 22/581 colds among those receiving antibiotic tablets on the first day, as against 87/338 among those receiving inert control tablets—3·8% as against 25·7%, a drop to one-seventh. In the adult industrial population, the proportion was one to nine, and this drop was evident in all the units of the investigation.

## Application of the Findings

(1) *In industry.*—Where a works has a Medical Centre, the antibiotic method is simple and consists of: (*a*) Preliminary sensitivity tests by a laboratory, results being carded and filed in the Medical Centre. (*b*) Substitution of the appropriate antibiotic tablets for whatever palliative has been used in the individual works concerned. (*c*) Taking care not to overdo the antibiotic, and that the approval of the patient's own doctor is obtained.

(2) *In practice.*—A. The antibiotic method is less easy to carry out because:

(*a*) Patients are not likely to report at a surgery on the first day, and, while the antibiotics will work even if given later, the whole idea is to forestall the attack by the patient's flora, and where that has begun the treatment is naturally at a disadvantage.

(*b*) Antibiotics should not be issued casually, nor should they be freely available to all and sundry.

An interesting point is that a number of practitioners have been treating some early influenzas with systemic antibiotics on purely empirical grounds, and some have expressed the opinion that complications have been markedly fewer. Initially severe cases have recovered more rapidly, albeit toxic, with this treatment than less severe cases which have trailed on with malaise and complications where antibiotics have not been used. This has been on purely experimental lines, but, if one assumes that the theory of the starting handle may apply to influenza also, fits into the picture.

B. Autogenous vaccines, however, if properly made, could be used a great deal more than they are. It must be emphasized that none but autogenous vaccines are likely to be of service, as the nasopharyngeal organisms of the general population are very heterogeneous. With the simple technique we used, these are easily made in the laboratory. The weekly dosage—0·1, 0·3, 0·5, 0·5 ml., &c., of a 500 million per ml. suspension—is a nuisance, but the real chronic cold sufferer will put up with anything that he hopes will help, and these are the cases which show most benefit. Several of our volunteers, after having two winters' injections, have been persuaded to try going the next winter without injections and have remained free, suggesting a build-up of immunity.

## Disadvantages

(1) *Autogenous vaccines.*—I know of no drawbacks apart from the tedium of weekly injections. A slight redness at site of inoculation was seen in some cases, but gave no trouble and subsided readily without treatment.

(2) *Antibiotic tablets.*—The only trouble was the incidence of "strawberry" tongue. This seems to be a form of idiosyncrasy as most volunteers were unaffected. It might persist for some time, although the cold itself had cleared up in forty-eight hours or less. The makers of the tablets say that the cause is not yet clear. An interesting point is that the school in our series had no trouble of this kind, which suggested a balanced vitamin diet though the manufacturers have found no connexion with vitamins but favour the glucose angle. The condition was usually mild, having little more than nuisance value except in a very few cases. Possibly reduction in dosage to less than the 15 mg. per tablet might be the answer. When this difficulty has been eliminated the way may be clear to the control of the common cold in industrial establishments.

*See also* Ritchie, J. M. (1958) *Lancet*, i, 615, 618.

## BOOK REVIEWS

**Cortisone Therapy.** Mainly applied to the Rheumatic Diseases. By J. H. Glyn, M.A.(Cantab.), M.D., M.R.C.P., D.Phys.Med. (Pp. x+162; illustrated; 21s. 0d.) London: Heinemann. 1957.

When important questions in a new domain of practical medicine remain controversial, and when the literature has become unwieldy, a monograph which critically examines available data can be immensely helpful. In "Cortisone Therapy" Dr. J. H. Glyn attempts an appraisal of the therapeutic value of cortisone, especially in rheumatoid arthritis.

This, however, is not the kind of review that will appeal to specialists. In the light of his own experience he considers the work and views of others, but usually does not tell us who they are: no references are given, and apart from a list of some well-known textbooks, reviews and articles—"for further reading"—there is no bibliography.

It is in fact a synthesis designed for general practitioners.

In an important chapter—"Practical Problems in Cortisone Therapy"—Dr. Glyn considers, among other things, how patients with rheumatoid arthritis are to be selected for prolonged cortisone therapy. He thinks it is indicated in some 15–20% of all cases. It is perhaps not made plain enough that relief is likely to decrease and danger to increase with the passing years.

A short chapter is given to intra-articular hydrocortisone in rheumatoid arthritis; and a well-illustrated and very helpful appendix on the technique of intra-articular injection has been provided by Dr. J. G. Bearn, Lecturer in Anatomy at the Middlesex Hospital Medical School. The use of local hydrocortisone in osteo-arthritis, bursitis, teno-synovitis and other soft tissue lesions, is discussed in a chapter on the use of cortisone in diseases other than rheumatoid arthritis.

The style is apt to be verbose: and his studious avoidance of the first person singular becomes a little tiresome. But with these minor criticisms, the book can be confidently recommended to general practitioners and hospital residents.

**Bronchopulmonary Diseases. Basic Aspects, Diagnosis and Treatment.** By 142 Authors. Edited by Emil A. Naclerio, M.D. (Pp. xxvi+956; illustrated; £8 17s. 6d.) London: Cassell & Co. Ltd. 1957.

This magnificently produced volume of close on a thousand pages consists of contributions upon bronchopulmonary disease from no less than one hundred and forty-two authors, many of whom are among the best known in the specialty. As Overholt states in his foreword, "The early publication in book form of papers prepared by many authors for an immediate outlet in a journal gives broader coverage than the usual type of book and can be more up to date". Indeed, this sentence epitomizes the mode of presentation here. Many distinguished contributors, such as Abbott, Auerbach, Banyai, Barach, Chamberlain, D'Esopo, Harkavy, Jackson, Janes, Lincoln, Mitchell and Samson, write upon the subjects they know best and others fill in the gaps, giving a bird's eye view of respiratory diseases which ranges from embryology to tracheotomy. By and large, the information is up to date and many of the chapters could hardly be bettered. Individual authors have evidently been given a free hand, and editing in the ordinary sense has not been attempted. For example, the chapter upon "The Pneumonias" is divided into three parts, namely a general classification (three pages, no references), chemotherapy in acute pneumonias (ten pages, four references) and lipoid pneumonia (six pages, sixty-two references). This unevenness, which prevails throughout, means that it cannot be used as a book of reference even in the United States, from which country nearly all the references derive. The reviewer was interested to see that no less than six pages are devoted to bronchitis (no references), which is more than usual for an American text book, but the prevalence and consequences of intermittent and chronic bronchial suppuration are still understated.

This tome contains so much information that at least part of it must appeal to anyone interested in disorders of the respiratory system. The unfortunate mode of presentation and the fragmentation into short chapters make it difficult to read. Perhaps it is best regarded as a collection of contemporary articles, almost any one of which is well worth reading on its own.

**Fluid Balance in Surgical Practice.** By L. P. Le Quesne, D.M.(Oxon.), F.R.C.S.(Eng.). (Pp. vii+140: 20s.) London: Lloyd Luke (Medical Books) Ltd. 2nd Edit. 1957

This admirable small monograph was reviewed in these columns some two and a half years ago and now a new edition has been called for and, apart from numerous minor emendations, differs mainly from the previous one in the inclusion of a chapter on fluid balance in children. There is certainly no shortage to-day of books concerning fluid balance and this is a good thing because as a subject it has been neglected for many years. This particular one makes a special appeal to the surgeon and it was indeed originally the prize-winning Moynihan Essay, the main burden of its thesis being the fluid and electrolyte balance of the post-operative patient.

The new chapter written by Dr. Webb provides an excellent epitome of fluid balance in childhood with a very proper underlining of the importance of conservatism at all times when infusing infants and children. Far too many neonatal babies have been drowned by the over-solicitous attention of house officers with intravenous drips; more than have succumbed to dehydration, for a baby at this time of its life is exceedingly well provided against the rigours of limited fluid intake. The rest of the chapter on the giving of fluid and electrolytes to children is clear, concise and thoroughly sound.

Le Quesne's book is pleasant to read, yet provides an excellent background to the newer scientific work in this field. There is a reasoned appreciation of the changes in fluid balance which occur during the administration of adrenal cortical hormones. There is a good account of the anti-diuretic hormone and potassium deficiency finds its place in this work without being unduly stressed as it has been in recent years. There is in addition sound advice concerning the management of renal failure, a problem much to the fore at the present time.

**The Anatomy of Congenital Pulmonary Stenosis.** By Sir Russell Brock, M.S., F.R.C.S., F.A.C.S.(Hon.). (Pp. xiii+114; illustrated; 30s. 0d.) London: Cassell & Co., Ltd. 1957.

Sir Russell Brock is well known as a thorough, fastidious and clear-thinking author and his book on "The Anatomy of the Bronchial Tree" is still a standard work of reference. In this new monograph he writes from an unrivalled experience in treating the condition and each aspect of the subject is considered, be it embryological, historical or that of comparative anatomy.

Sir Russell was the pioneer of the direct approach for treating pulmonary stenosis and perforce had to acquaint himself with the various anatomical varieties which could be encountered. The wealth of illustrations in this monograph demonstrates the various types of infundibular and valvular stenosis which may be encountered and also the secondary changes which take place in the rest of the cardiovascular system. The principles of operative repair naturally figure largely in the text, but this is a work which deals as thoroughly with the anatomy and physiology of the condition as it does with its surgical correction. Many readers may be surprised to find that Sir Arthur Keith had written so widely on this subject and his admirers will be delighted to see a particularly attractive photograph of him forming the frontispiece of this book. Evidence is assembled to show that a controlling mechanism exists in the musculature of the right ventricular outflow tract which controls the flow of blood. This is based partly on the work of Keith and also on observations made on the living patient by the present author.

**Principles of Surgical Physiology.** By Harry A. Davis, M.D., C.M., F.A.C.S. (Pp. xiv+841; illustrated; £7 7s. 0d.) London: Cassell & Co. Ltd. 1957.

This large book of some 800 pages sets out to cover a very wide field of physiology, primarily that involved in surgical practice.

There is of course no such subject as surgical physiology, or at least there should not be; physiology remains the same whether it is read by surgeon, physician or physiologist, but it is possibly a convenience to gather together into one work the sort of physiology which is of most importance to the surgeon. Here will be found good introductions to such subjects as water and electrolyte metabolism, wound healing, tissue transplantation, the pancreas, spleen and so on. There are very well-selected references at the end of each chapter.

This is not a book to be put in the hands of every student, it is rather one which should be placed in the library or the department of surgery.

The book is written much more in the style of a surgical than of a physiological work. This is essentially a work of reference which provides an enormous amount of basic information and is likely to continue through many editions in the future.

**Introduction to Clinical Endocrinology.** By A. Stuart Mason, M.A., M.D., B.Ch.(Cantab.), M.R.C.S.(Eng.), M.R.C.P.(Lond.). (Pp. viii+192; 22s. 6d.) Oxford: Blackwell Scientific Publications. 1957.

This is a brief neat little book and contains precisely what the title states. It is an introduction to clinical endocrinology and there are no references, although the work is well up-to-date and appears to be completely free from the errors which so often appear in a first edition.

There is a good account of the hypothalamus and the anterior and posterior pituitary. The thyroid receives some thirty pages out of the total, which is right in so far as this is the one endocrine gland which provides more clinical material than all the others. The adrenals are well reviewed and primary aldosteronism finds a place in this chapter. The testes and ovary are both discussed in neat little essays and treatment is well described, doses always being clearly indicated.

This is a book primarily written for the newly qualified doctor who wishes to understand more about the subject of endocrinology as he sees it in his patients, but it serves equally well as an introduction for the final year medical student. It is well printed and bound and certainly not expensive at 22s. 6d.

**Benjamin Waterhouse and the Introduction of Vaccination. A Reappraisal.** By John B. Blake. (Pp. 95; illustrated; 32s. 0d.) Pennsylvania University Press. London: Oxford University Press. 1957.

In July, 1800, Benjamin Waterhouse, by inoculating his son with cowpox virus received from England, introduced the practice of vaccination into the United States. Since the latter part of the nineteenth century Waterhouse has been regarded as one of the most notable pioneers of preventive medicine in America. This latter-day praise contrasts strangely with earlier neglect, which has generally been attributed to the antagonism of Waterhouse's contemporaries, antagonism attributed variously to his religion, politics, scientific qualifications or skill in controversy.

This book gives a detailed history of the controversy based on a new analysis of contemporary letters and newspaper files. The picture of Waterhouse that emerges is not only of a controversialist writing numberless letters to the Boston papers attacking his professional colleagues, but also of a would-be monopolist, anxious to reserve the distribution of cowpox virus to those who were prepared to share the profits with him and distribute it no further.

Apart from the principal story the book is interesting for its revelation of the methods of medical controversy 150 years ago. The numerous quotations are fully documented in 17 pages of notes, and there are three illustrations of letters; many general readers would surely have preferred a portrait of the "hero". But at 32s. 6d. the book can hardly be for the general reader.

**The Early Diagnosis of the Acute Abdomen.** By Sir Zachary Cope, B.A., M.D., M.S.Lond., F.R.C.S.Eng. 11th edit. (Pp. 188; illustrated; 18s. 0d.) London: Oxford University Press. 1957.

This wonderful little book first appeared thirty-six years ago and Sir Zachary Cope has now almost entirely rewritten it and provided new illustrations. This book presents exactly the information which its title promises and does it so clearly and thoroughly that it is as well suited to the medical student as to the specialist in surgery. Certainly it has a particular appeal for the general practitioner and it would be hard to find a book which distils more wisdom more clearly in so few pages. The Oxford University Press are also to be congratulated on making the book so much more attractive in its latest edition.

**Artificial Insemination in the Human.** By A. M. C. M. Schellen, M.D. (Pp. xii+420; illustrated; 72s. 0d.) London: Cleaver-Hume Press. 1957.

This book covers the entire field from the history of A. I. to the ethics of A.I.D. It quotes everything everyone has ever done or said on the subject, to the embarrassment of many whose *obiter dicta* of past years were best forgotten. It is an anthology of the subject rather in line with Sutton's "Diseases of the Skin", and gives at the end of each chapter a complete list of world references. The indications for A.I.H. are given briefly but completely, including retrograde ejaculation, which has been dealt with successfully by Hotchkiss and others. In the indications for A.I.D. the author rightly points out the

great difficulty in declaring a case of gross oligospermia infertile to the point of sterility and hence advising donor insemination. In a series of cases elsewhere pregnancies have been reliably reported from counts as low as 500,000/ml. It is interesting to note the replacement of the cumbersome term oligozoospermia by oligospermia and the substitution of hypospermia for deficient volume.

There follows an excellent and comprehensive chapter of 68 crowded pages on the technique of A.I. The reason for the poor results in A.I.H. is perhaps not sufficiently stressed—it is of course entirely due to the poor quality of the semen. A.I.H. makes the best use of a poor specimen. Ways of improving these results are enumerated, stress being placed on the possibilities of freezing repeated "split" ejaculates, in cases of oligospermia, and finally thawing and pooling to build up a more nearly fertile specimen. Centrifuging is mentioned here and some workers still report on it enthusiastically but most have discarded the device, preferring to employ the first part of "split" or partitioned ejaculates.

As to collection of semen specimens, epididymal puncture is dismissed as rarely successful and so is vesicular massage, but the latter can be properly managed if the technique is understood and must remain until electrical induction is perfected and the apparatus made less costly. The dangers and advantages of the semen bank and donor pool, largely an American idea, are recounted. The practical part of the book ends with the timing of ovulation and the risks resultant on errors of technique.

The second part of the book is largely devoted to the vexed subject of A.I.D. and, following the recent controversy in England, will clearly need a new chapter. In turn it deals with the choice and selection of the donor, precautionary measures for the protection of the specialist and the consenting parties and the many and varied forms used by specialists all over the world are printed. These make interesting reading. A valuable chapter is given to comparison of adoption with A.I.D.; even the Press reactions of different countries are included.

**Connective Tissue.** A Symposium Organized by The Council for International Organizations of Medical Sciences. Edited under the direction of R. E. Tunbridge. (Pp. xii + 371; illustrated. 42s. 0d.) Oxford: Blackwell. 1957.

This symposium was held in London in 1956 under the auspices of the Council for International Organizations of Medical Sciences. Some thirty participants attended, and their contributions and group discussions are given *in extenso* in this monograph.

In general, the contributions centred mainly upon biochemical questions, and more particularly on the origins and constitution of the various fibrous elements and the ground substance of the soft connective tissues. Many of them are highly specialized, but several, notably those of Fitton Jackson, Schwarz and Robb Smith, which deal with the morphology and differentiation of the various types of fibre, will be of particular interest to pathologists and to clinicians concerned with rheumatic diseases.

The book provides an authoritative review of fundamental work in a field of medicine that in recent years has attracted particular attention as a result of efforts to establish a nosological entity from the "collagen diseases". Its perusal makes manifest the great progress that has been made in knowledge of the soft connective tissues since electron-microscopy and the newer biochemical tehcniques of protein chemistry have been applied to its study.

**Chronic Illness in the United States.** Volume 1: Prevention of Chronic Illness. Commission on Chronic Illness. (Pp. xxii+338; 48s. 0d.) Harvard University Press. London: Oxford University Press. 1957.

This book fulfils a useful purpose in drawing attention to the clinical, social and economic significance of chronic disease perhaps better designated, disease of chronicity. The important aspects of prevention, care and rehabilitation of the disabled is given prior place with good effect. This is the first volume of a 4-volume report dealing with chronic illness in the United States. The promotion of health, the prevention of selected chronic diseases such as arthritis and rheumatism, cardiovascular disease, tuberculosis, cancer, diabetes and blindness, all receive due attention and certain conclusions and recommendations are made which are extremely apt and helpful.

The book should be of great value to medical and social workers in this sphere and the suggestions made for further research are extremely helpful.

# Section of Pædiatrics

President—A. Doyne Bell, M.A., D.M., F.R.C.P.

[*October* 25, 1957]

## DISCUSSION ON THE MOUTH-BREATHER

**Mr. E. Gwynne-Evans** (London):

*The Mouth-breather and the Muscular Seals of the Oral Cavity*

Nasal breathing depends on the patency of the nasal passages and on the orofacial muscles closing and sealing off the oral cavity from the nasopharyngeal airway.

Mouth breathing due solely to gross nasal obstruction is comparatively rare; treatment is usually straightforward, depending on the recognition and removal of the cause. Mouth breathing due primarily to failure of the orofacial muscles is relatively common; little or no nasal obstruction may be present; lines of treatment vary; most are unsuccessful.

This paper is devoted to the mechanisms operating the anterior and posterior seals of the oral cavity in breathing and feeding. The functions of breathing and feeding are inseparable in any consideration; brief references will be made to:

(*a*) The evolutionary history of the air and food passages, the jaw and facial muscles.

(*b*) The developmental anatomy of the air and food passages; the face and neck region.

(*c*) The changes in orofacial behaviour that take place as the central nervous system matures.

*The Comparative Anatomy of the Air and Food Passages*

The researches of Sir Victor Negus show that differences in structure among the species are associated with varying requirements. In most mammals, the tongue lies flat in the mouth; the larynx lies just behind the mouth well forward in the neck and is related to the level of the basi-occiput, not to the cervical vertebræ, as in man. Mammals depending on their sense of smell have a special fibrocartilaginous flap—the epiglottis—standing up in front of the laryngeal aperture. This flap either overlaps the free margins of the soft palate as in deer, or extends upward into the posterior opening of the nasal channels as in whales and dolphins. This arrangement effectively prevents breathing through the mouth and ensures the drawing in of air over the olfactory nerve endings. In man the jaws lie under the cranium; the tongue is "bunched up", arched and displaced backward so that it curves downward into the pharynx. The larynx lies below and at right angles to the line of the mouth, opposite the cervical vertebræ. The epiglottis is separated from the soft palate and the seal to prevent oral breathing is lost. However, the soft palate lies passively over the posterior convex surface of the tongue and in certain circumstances close coaptation of the soft palate and tongue will prevent mouth breathing.

Food has to be transferred from the mouth to the gullet past the larynx with a minimum of interference to breathing.

In man the epiglottis is tipped over the aperture of the larynx to form a chute for the passage of the food. Breathing ceases momentarily when the sphincteric girdles of muscle close the nasopharyngeal and laryngeal apertures respectively and the sphincter surrounding the upper end of the œsophagus relaxes to allow the food through. As swallowing is intermittent and rapid there is very little interference with breathing. In herbivoræ the epiglottis is well developed, overlapping the soft palate and its lateral folds. The upstanding lateral margins of the epiglottis give protection to the laryngeal aperture. For long periods semi-liquid food passes on either side of the larynx almost continuously into the gullet between the ary-epiglottic folds and the lateral walls of the pharynx. Overflow into the larynx is prevented, interference with breathing is avoided and the sense of smell, particularly for the detection of enemies, is thus in use throughout the feeding period. Although man is never dependent on the sense of smell, the demand for continuous and uninterrupted nasal breathing when feeding is just as insistent in early infancy. The rhythm of suckling once initiated tends to continue for minutes at a time unless deliberately interrupted. Free and continuous nasal breathing throughout the suckling period is therefore vital.

*The Functional Anatomy of the Infant Oral Cavity*

In infancy the vertical space between the gums is filled by the arched tongue, which contacts the inner surface of the cheeks, the hard and soft palate. The anterior margin of the tongue is broad; there is no tip and it cannot be protruded far or swept from side to side; it is used exclusively for pumping and squirting milk into the pharynx in suckling or for passing fluids otherwise placed in the mouth by sliding them backward and downward into the pharynx.

The high level of the tongue in the infant oral cavity is associated with a high level of the larynx in the neck. Although there is no actual contact of the epiglottis with the soft palate, the close proximity of the larynx to the mouth enables the upstanding lateral folds of the epiglottis to direct the flow of milk around the larynx without inundation of the glottic aperture. The close relationship of the tongue and palate is necessary for suckling. Slow motion cine films have shown that a rubber teat placed on the dorsum of the tongue is repeatedly compressed against the hard palate and rolled out from before backward by successive waves of contraction in the transverse fibres of the tongue. A cine radiographic loop of film showed a rhythmical tensing of the soft palate against the posterior surface of the tongue. Its action seemed to direct the passage of the milk downward toward both lateral food channels of the pharynx and, at the same time, to maintain a free nasopharyngeal airway for continuous breathing. There were times, however, when the soft palate flicked upward as if to close off the nasopharynx, but, on the whole, the manner of feeding and breathing seemed to resemble very closely the feeding and breathing behaviour of herbivorae as described by Negus. Only with the swallowing of accumulated fluids and later a bolus of food, are the sphincteric systems of the pharynx and larynx utilized.

The lips take no active part in suckling other than forming an effective seal between the infant oral cavity and the breast or rubber teat of a feeding bottle. At rest, they relax; they may or may not be in contact. Lip closure is not an essential requirement; nasal breathing is the rule because the oral route is effectively sealed by the muscular barrier set up by the coaptation of the tongue and palate.

*The Developmental Anatomy of the Child's Oral Cavity and Neck Region*

As the infant grows up an elongation of the lumbosacral segment of the vertebral column and a general increase in the size of the pelvic cavity allow the abdominal viscera to descend. At the same time, the levels of the shoulder girdle and thoracic cage descend to reveal the cervical segment as a neck. The viscera of the neck, viz. the tongue and larynx, are also lowered. The tongue, no longer needed for suckling and already curving backward and downward into the pharynx, descends with the larynx far enough to make way for the downward growth of the maxilla from the base of the skull. The lower level of the tongue and larynx in the neck allows the tongue more freedom to move in the oral cavity for the gathering and passing of food between the erupting teeth which come gradually to fill the vertical space between the margins of the jaws.

In some children, the seal between the soft palate and tongue is preserved; in others, the tongue falls away from the palate and the seal is broken. Should the lips be apart and the mouth be open, in the former case nasal breathing will be the rule, in the latter, mouth breathing will supervene in addition to nasal breathing.

*The Evolutionary History of the Jaw and Facial Muscles*

In some activities of the orofacial muscles, as in suckling, sipping or drinking, they behave in a rhythmical manner as do other muscles of the vegetative or visceral system. In other activities, as in speech, they behave in a highly versatile and complex manner as do other muscles of the somatic system. Referring to the evolutionary history of the jaw and facial muscles, it is significant to find that the branchial muscles of the fish, although striated, are innervated through special cranial nerves belonging to the visceral motor system, not like other striated muscles which are supplied through the somatic nervous system. Higher up the evolutionary scale it is seen that much of the striated visceral musculature has abandoned the gut lining to serve the jaws. Other surviving branchial elements serve a series of aberrant functions as shoulder, neck and facial muscles. In land vertebrates, the constrictor of the hyoid is the only superficial muscle remaining in the neck region. In mammals, it extends as a thin sheet over the surface of the head to form the facial muscles, concentrating in bands round the orbits, outer ears and lips. The purpose of the facial muscles is primarily to control these apertures—not by sphincteric action but by an opening and closing arrangement of the muscle fibres. Man, in common with herbivoræ, has well-developed muscles forming the lips and cheeks. The history of their visceral origin is linked with their main purpose—that of receiving and keeping food in the mouth for chewing. Other functions are grafted on later as a side-effect.

*Changes in Orofacial Behaviour as the Central Nervous System Matures*

From the works of Tinbergen and others, it is now realized that groups of muscles are co-ordinated from within an hierarchically organized central nervous system to carry out special movements for locomotion, feeding or hunting &c., which are characteristic of the species and necessary to the maintenance of the individual. Experiments have shown that they are innate and "triggered off" by appropriate stimuli from the outside world. Once the in-born or unlearnt response is modified, however, and a more precise adaptation to environment is made, learning processes are involved. As these progress, it soon becomes difficult to distinguish between unlearnt and learnt behaviour.

Suckling is an innate pattern of behaviour. The taking of food from a spoon, the thrusting of food by the hand into the mouth, the biting and chewing of food—all require different patterns of muscle co-ordination concerned with the basic function of feeding. They are not learnt, but appear in succession as fresh neuromuscular pathways are opened up by the normal processes of maturation. With practice, more precise movements are achieved automatically; modifications of feeding behaviour acceptable to good-mannered society are learnt—and these, like all cultural patterns, come the hard way.

In early infancy, the tranquillity of the face is frequently disturbed by emotional outbursts when all the muscles attendant on the lips contract as an entire group without discrimination to stretch the mouth widely open. Passive relaxation allows the lips to return to their usual position of rest; they may or may not lie in contact; the facial mask is expressionless and one of innocent repose. Total behaviour, typical of an immature central nervous system, gives way to selective behaviour in which the lips may assume a variety of shapes. It is difficult to say how far these movements are "in-born" and come from "within" in response to a particular situation or are acquired by imitating other individuals. However, as mental attention is directed toward the orofacial muscles their behaviour is increasingly modified to express the finer feelings and the growing intellect. The unfolding of inherited characteristics brings about further modifications of the facial mask, and it soon becomes even more difficult to say how far the features should be accredited to nature or to environment.

Mental attention constantly invokes lip closure, but in repose the lips will relax to their normal position of rest—in contact or apart; if apart, it is usual to find that as the personality and character of the individual develop, lip closure is eventually embodied in the more mature facial mask of the growing adult without the need of conscious effort. There are, of course, exceptions to this desirable state of affairs, for instance, the personality and character of the individual may not contribute toward lip closure in repose; or structural imperfections, such as a short everted upper lip or a marked discrepancy in the antero-posterior relationship of the jaws and teeth may make lip contact difficult or impossible to achieve.

*Clinical Assessment of Facial Appearances*

Some faces in repose embody lip contact; their outlook on life appears attentive. Some do not embody lip contact; the lips lie more naturally apart than together; moreover, the mouth may be open, often widely.

The lack of awareness in the facial appearance of the last-mentioned children has been attributed to dullness of intellect secondary to adenoid overgrowth, nasal obstruction and inadequate oxygenation of the tissues. Experience shows, however, that a low level of mental ability is not usually found, that the adenoids are not necessarily causing nasal obstruction and that the open mouth is not always indicative of mouth breathing.

This paper is concerned with other explanations of the clinical picture. At one time, the jaw muscles were wrongly classified with the anti-gravitational muscles; it was thought that the open mouth was due to lack of resting tonus in the jaw muscles and a consequent sagging of the mandible. General measures and special exercises prescribed with the idea of increasing muscular tone failed to maintain a closed mouth at rest. Again it was thought that the open mouth was due to a faulty habit of co-ordination among the orofacial muscles. Attempts were made to re-educate the muscles in correct habits of co-ordination. Special exercises in the form of games were prescribed to encourage a proprioceptive sense of contact between the lips. Dental appliances such as the Andresen monobloc (a form of intra-oral screen) were employed to provide the child with a sensory pattern or a "mental image" of a closed mouth. These measures also failed to inculcate a habit of lip and mouth closure at rest.

It soon became apparent that the facial mask, whatever the appearance, is innate to the individual and resists change by any means.

No two faces are exactly alike except perhaps those of identical twins. Yet, there are many "types" of faces with similar variation of soft tissue morphology that come well within the widely accepted limits of what might be called "a normal face". The opinion is now held that the concept of "normal variation" should be broadened to include the facial type whose mouth is usually open when the child is at rest. In this type it is not that the mouth cannot be kept closed at will but that when the face is in repose, the jaw and facial muscles will inexorably relax to the open position which, as Professor Ballard states, is the "innate resting position" and therefore normal for the individual. Perhaps the truth of this concept might be better understood if the converse type of face be considered. In this case, it is natural for the lips to be together and the mouth closed in repose; constant mental effort will be necessary to keep the lips apart and the mouth open; the closed position is innate to the child and therefore normal for him.

Facial appearances give little or no indication of mouth breathing or of nasal obstruction. Taking the "open mouth" type of child first; an inherent coaptation of the tongue and soft palate will sometimes persist and still prevent mouth breathing. Mouth breathing will only occur when (*a*) the soft palate is elevated from the tongue in order that breaths may be drawn deliberately through the mouth because of nasal obstruction, or (*b*) the tongue lies naturally away from the soft palate whether nasal obstruction is present or not. It is significant that when nasal obstruction is present, correctly diagnosed and treated, with restoration of a free nasal airway, this type of facies remains unchanged apart from any influence the progress of maturation may have later on facial appearances. Referring to the "closed mouth" type of child, an inherent contact of the lips will prevent mouth breathing. The presence of nasal obstruction, however, is not ruled out; an intermittent and often imperceptible parting of the lips and separation of the tongue and soft palate will allow adequate mouth breathing if necessary. It is again significant that when nasal obstruction is present and removed, a closed mouth with lip contact is immediately resumed in this type of child.

Mouth breathing must be sought for in every child and if found to be present, the primary cause should be ascertained. The best way to test for mouth breathing is to hold in front of the mouth a cold polished metal tongue spatula to obtain condensation of breath and visual proof. The capacity for nasal breathing can be assessed in the same manner. Anterior rhinoscopy is necessary to reveal the state of the mucosa and to exclude the commonest cause of persistent anterior nasal obstruction, viz. chronic œdema of allergic origin. Soft tissue lateral radiographs of the entire pharynx are necessary to demonstrate the presence of adenoids, possible overgrowth and obliteration of the post-nasal space; also, to show the position and relationship of the tongue and soft palate at rest.

*Conclusion.*—It is preferable to institute measures to ensure healthy and free nasal passages than to worry unduly about facial appearances and to submit the child unnecessarily to the wearing of dental appliances, to tedious lip exercises or to the injustice of constant admonitions to keep the mouth and lips closed.

BIBLIOGRAPHY

BALLARD, C. F. (1953) *Trans. europ. orthod. Soc.*, p. 145.
—— (1955) *Dent. Practit.*, **6**, 80.
GWYNNE-EVANS, E. (1951) *Brit. dent. J.*, **91**, 135.
—— (1954) *Trans. europ. orthod. Soc.*, p. 20.
—— (1956) *Med. Pr.*, **235**, 246.
——, and TULLEY, W. J. (1956) *Dent. Practit.*, **6**, 222.
NEGUS, V. E. (1949) The Comparative Anatomy and Physiology of the Larynx. London.
—— (1953) *Speech*, **17**, 58.
RIX, R. E. (1948) *Trans. europ. orthod. Soc.*, p. 13.
ROMER, A. S. (1949) The Vertebrate Body. Philadelphia and London.
TINBERGEN, N. (1951) The Study of Instinct. Oxford.
TULLEY, W. J. (1956) *Amer. J. Orthodont.*, **48**, 11.
WHILLIS, J. (1946) *J. Anat., Lond.*, **80**, 115.
WOOD JONES, F., ed. (1946) Buchanan's Manual of Anatomy. 7th edit. London.

**Professor C. F. Ballard** (London):

*Mouth Breathing*

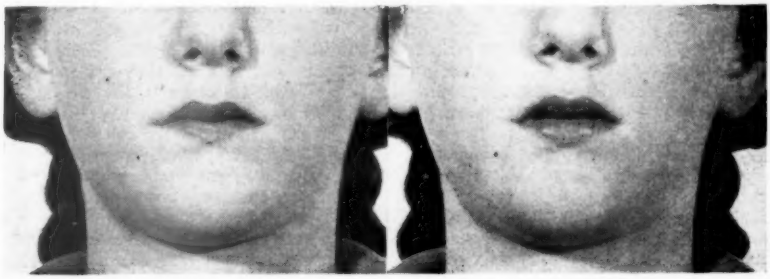
In 1929 Brash said: "There is no satisfactory proof that the presence of adenoids, the diminution or absence of nasal breathing or the constant habit of mouth breathing can affect the form of the jaws or the position of the teeth in any of the ways that have been suggested. It has still to be proved that there is any significant correlation between the presence of adenoids and the incidence of deformities of the jaws and palate."

For more than fifteen years a group of us have been studying the relationship between (1) jaw form, (2) soft tissue morphology and (3) the behaviour of soft tissue morphology in relation to malocclusions and upper respiratory conditions. Our observations have not only confirmed what Brash said, but have by inductive reasoning demonstrated quite clearly that mouth breathing does not produce deformities of the jaws and malocclusions, and does not result in the development of the adenoidal facies. Our studies necessitated detailed classification of variations of the form of the jaws, of the morphology of soft tissue, of the patterns of activity of the soft tissues in the production of anterior and posterior oral seals, and in mastication, speech and expressive behaviour.

Our longitudinal studies based on this classification have shown that the orofacial morphology remains remarkably constant during growth. It does not change in the ways that would be necessary to produce an adenoidal facies, with the associated deformities, as a result of nasal obstruction and mouth breathing. Further, detailed classification has shown that as we bring more individuals into a cross-sectional study distinct types fade and the picture becomes more that of a smooth distribution of variations.

In my view this is an indication that we are in fact not dealing with abnormalities arising as a result of environmental conditions but with variations determined by inheritance.

It would be advantageous at this stage to describe some of the variations of soft tissue posture and activity that Mr. Gwynne-Evans has mentioned. Firstly the lips-closed posture or, as it is now called, competent lip morphology. The individual maintains an anterior oral seal without muscular effort (Fig. 1A). The mandible is in the innate postural position



A B

FIG. 1.—Competent lip morphology. A, Maintaining anterior oral seal with muscles in their innate posture. B, Mandible and tongue dropped from innate posture to produce an oral airway.

and the muscles of facial expression are similarly postured. The tongue almost fills the oral cavity and posteriorly contacts the soft palate and maintains a posterior oral seal. If individuals with such a combination of morphological features have nasal obstruction an oral airway is produced by dropping the mandible to part the lips (Fig. 1B) and by dropping the tongue away from the soft palate. It does not matter for how long they have to maintain mouth breathing, they do not develop an adenoidal facies or lips-apart posture.

Now for the lips-apart posture or so-called adenoidal facies (Fig. 2B). The mandible



A B

FIG. 2.—Incompetent lip morphology. A, Circumoral contraction to produce an anterior oral seal. B, Lips apart, mandible and facial muscles in innate posture.

gain is in the innate postural position and the facial musculature is in its innate posture. In order to produce an anterior oral seal these individuals have to contract the circumoral muscles to a degree which might be so slight that it is not detectable by the uninitiated observer, or it may be so extreme that it spoils the individual's facial appearance (Fig. 2A). This open-lip posture is not due to lack of tonus, it is not produced by dropping the mandible from the innate posture and does not arise as a habit because of the constant necessity for oral breathing. Furthermore as has been previously reported (Ballard, 1952; Gwynne-Evans and Ballard, 1948) the majority of individuals with this lips-apart posture are not mouth-breathers because the posterior oral seal is intact. This can be demonstrated clinically and radiographically. Still further support for our conclusions comes from our early attempts at re-education as we called it; these failed and it was because they did so, uniformly, that we delved more deeply into the physiology and genetic background of posture and motor activity (Ballard, 1955).

Our observations have demonstrated in detail the morphology associated with the findings of Warwick James and Somerville Hastings (1932) that the open lip posture is not necessarily associated with mouth breathing. Warwick James and Somerville Hastings regarded the tongue soft palate contact as a posterior oral sphincter. It is this open-lip type which results in such statements as "the adenoid facies may be met with in children without adenoids".

These facts on the relationship of variation of soft tissue morphology to mouth breathing should be enough in themselves to destroy the theory that mouth breathing can produce narrow nasal passages, underdevelopment of the mouth and general arrest of growth, V-shaped alveolar arches and crowded teeth. Unfortunately, however, these varieties of skeletal morphology do occur together and frequently in association with the lips-apart posture. Therefore further discussion is necessary. As has just been stated, however, there is no cause and effect link with mouth breathing.

Longitudinal studies of the growth of the facial skeleton have been in progress for a good deal longer than our longitudinal studies of soft tissue development partly because of the ease with which the patterns could be recorded radiographically. Brodie (1940) reported on a serial study of growth of the face and his conclusions indicate that even in cases of extreme variations of the skeletal morphology, the so-called abnormal, the patterns were established soon after birth and thereafter developed in an orderly manner, the general pattern of each case remaining the same.

Our longitudinal studies and assessments of morphological types confirm these findings. We do not find any particular type of morphological pattern associated with mouth breathing; all types may suffer from chronic nasal obstruction. We do not see a change in shape or size of the jaws with chronic nasal obstruction and mouth breathing as would be expected, and we do not see changes towards a "normal" after relieving nasal obstruction. Further and strong support surely comes from reported cases of complete nasal atresia—to quote Thomson *et al.* (1955): "It is noteworthy that this complete atresia of the nose even with entire mouth breathing does not entail the chest deformity, narrow nostrils, alar collapse, deflection of the septum and changes in the ears which are frequently attributable to partial nasal stenosis."

With regard to the chest deformity it is quite possible that there may be an association between the type of facial morphology which has been labelled adenoidal and flat chest with winged scapulæ because the open-mouth posture may be shown by investigations in progress at the moment to be more common in the individuals high in ectomorphy.

Putting all the facts together, and they include evidence not mentioned on the inheritance of orofacial variations, I would state quite definitely that orofacial morphology is mainly inherited and is not so amenable to environmental influences as the mouth-breathing adenoidal facies concept requires. If this is so, what is our approach to treatment both for the open-lip position, the true mouth-breather and the malocclusions associated with these variations?

To deal firstly with the malocclusion that may be present. Prominent upper incisors may result from a combination of the following inherited features in a typical case.

(1) Open-lip posture.

(2) Crowding in the maxillary arch.

(3) A skeletal morphology which has resulted in the mandibular dental base being post-normal to the maxillary dental base.

The consequence of this combination of features is that the lower lip is behind the upper incisors at rest and in many cases an anterior oral seal is produced by contracting lower lip against tongue, the upper lip being comparatively inactive.

The orthodontist cannot change growth patterns and therefore cannot change jaw relationship. What can be done, however, is to bring the upper incisors lingually and inside the lower lip after reduction of the number of teeth in the maxillary arch. This treatment is most satisfactorily carried out by the extraction of the upper first premolars when they erupt (at about 10 to 11 years). Then by orthodontic treatment the upper incisors are brought inside the lower lip enabling the individual with incompetent lip morphology to produce an anterior oral seal with far less muscular effort, and in some cases greater use of the upper lip results. However, in other cases the innate open-lip posture remains and some training is required to establish a habit posture of lip seal. It is important to differentiate between innate posture and a habit posture (Ballard, 1955) if the aim of the training is to be appreciated.

Our clinical approach is as follows: We have found, as Mr. Gwynne-Evans has said, that an attempt to induce the maintenance of an anterior oral seal as a habit posture in young children is frustrating both to the child and the parents. Lip exercises and games are of little avail and a waste of time. The child is left alone to develop naturally until the time that orthodontic treatment is indicated. Following orthodontic treatment a fair percentage of children by the application initially of some conscious effort induce a habit posture of lip closure which is later quite possibly maintained reflexly as a result of sensory contact of lips. In some individuals the tongue comes into the production of an anterior oral seal making contact with the lower lip. In other individuals the degree of incompetence is such that they have to apply considerable conscious effort in the maintenance of an

anterior oral seal. Many of these report that they know their lips do not stay together at night and in fact in such cases they are frequently apart during the day, particularly when conscious effort relaxes in moments of interest or excitement, &c. In the extreme, there are the cases in which the degree of incompetence is such that the maintenance of an anterior oral seal requires a greater effort than can be maintained consciously, such a muscular effort in fact spoiling the facial appearance.

To sum up: In these cases the open-lip posture is not a habit but the lips-closed one is, and as the degree of incompetence increases so the degree of mental effort to produce the habit is greater. At the same time, age and environment of the individual have to be taken into account when suggesting the application of conscious effort in the production of the habit posture.

Lastly there is the case of the true mouth-breather due to inherited incompetence of both anterior and posterior oral seals. If the physician or otorhinologist believes that oral respiration is a contributory factor in the maintenance of an upper respiratory infection then it is possible to control nasal respiration during the night by means of the insertion of an oral screen as has been illustrated by Scott-Brown (1952) and many dental textbooks, or the monobloc appliances which will fit on the lingual sides of upper and lower dental arches round the tongue induce mouth closure reflexly in some cases.

It is frequently stated that long-standing nasal obstruction results in loss of instinct for nasal respiration and the individual continues to mouth-breathe and has to be re-educated. This is not so. The idea has arisen because, when nasal obstruction is cleared by the removal of adenoids, in those cases with the open-lip posture, the individual still has the open-lip posture post-operatively. When adenoids are removed for the reason that the child is mouth-breathing as diagnosed from the lips-apart posture, loss of instinct is given as the reason for the persistence of the lips-apart posture. However, in those cases of nasal obstruction with the innate lips-closed posture, no re-education is required. The individual reverts immediately to nasal respiration and it is so even with the open-lip posture if the posterior oral seal is innately competent. In 1955 I discussed the biological background to instinctive and habit orofacial behaviour and gave my reasons for believing that habits do not displace innate patterns in the central nervous systems as readily as the loss of instinct theory would require.

I have already mentioned that a cross-sectional study might show a correlation between the lips-apart posture and the body type high in ectomorphy. It might also be possible to demonstrate a correlation between the lips-apart posture and the incidence of asthma, upper respiratory infection and even appendicectomy and myopia. This may seem on the face of it absurd but I should like to refer you to a paper by Wallis (1953). He investigated the connexion between post-normal occlusion and general health, enlarged tonsils and adenoids, chest diseases and deformities, &c. Post-normal occlusion is in our population frequently associated with the lips-apart posture so his conclusions are of interest here. Briefly, he found a correlation between post-normal occlusion and a greater tendency to suffer from birth onwards from a large number of disorders. From this correlation he postulated a general biological inferiority of the post-normals. He reasoned that this might explain why collections of skulls of 400–500 years ago showed a low percentage of malocclusion. Those with post-normal occlusions being biologically inferior did not survive the very high infant mortality rate. In my opinion further investigations on these lines might be profitable.

## Conclusion

In my view the theory of adenoidal facies has resulted from a purely subjective approach and a lack of knowledge of the extent of inherited variations. I should also like to be so bold as to suggest that if our observations are sound and can be applied to the remainder of the body then much time is probably being wasted and feelings of frustration induced in parent and child by treatment or training and perhaps unnecessary surgical procedures performed because the extent of genetically determined variations in our population is not appreciated. Attempts are being made to change innate characteristics of posture and motor behaviour and these impose physiological and mental strain on the individual.

## REFERENCES


Ballard, C. F. (1952) *Med. Pr.*, **228**, 347.

—— (1955) *Dent. Practit.*, **6**, 80.

Brodie, A. G. (1940) *Amer. J. Orthodont.*, **26**, 741.

Gwynne-Evans, E., and Ballard, C. F. (1948) *Dent. Rec.*, **68**, 1.

James, W. W., and Hastings, S. (1932) *Proc. R. Soc. Med.*, **25**, 1343.

Scott-Brown, W. G. (1952) Diseases of the Ear, Nose and Throat. London.

Thomson, StC., Negus, V. E., and Bateman, G. H. (1955) Diseases of the Nose and Throat. 6th edit. London.

Wallis, H. R. E. (1953) *Dent. Rec.*, **73**, 519.

[*November* 22, 1957]

**Three Cases of Cherubism** (One previously shown in January 1954).—A. WHITE FRANKLIN, M.B., F.R.C.P.

*Case I.*—R. M., male, born 10.6.48. Noted by his mother to have a swollen face at the age of 3 years. When seen aged 5 years he had the typical facies of cherubism and had shed his permanent lower central incisors. His case was reported to the Section in 1954 (*Proceedings*, **47**, 543). Since then the swelling has somewhat diminished, but there is gross deformity of the hard palate with indistinct speech (Figs. 1, 2 and 3).



FIG. 1 (*Case I*).—Shows swelling of jaws and elevated appearance of eyeballs.

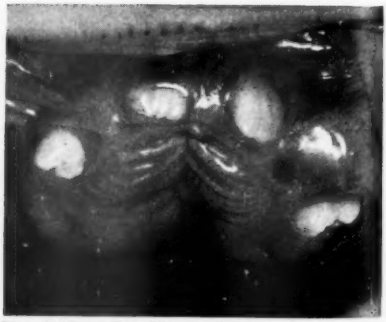


FIG. 2 (*Case I*).—Shows absence of permanent teeth and downward swelling of the maxillæ.



FIG. 3 (*Case I*).—Shows typical fibrous dysplasia of both jaws with irregularity of the few remaining teeth.

*Family history.*—In 1954 the mother reported a negative family history. She now says that her own father had a very full face as did she herself in childhood. Her father could pick teeth out of her jaw with his fingers. X-ray of the mother's lower jaw shows some areas of rarefaction which are compatible with past fibrous dysplasia. Her eldest child, a girl of 13 years, is normal, but another daughter (Case II) is developing cherubism.

*Case II.*—G. M., female, born 18.9.53. She is in other ways a normal, healthy girl. When examined in January 1954 she looked normal. X-rays of the jaws were normal. From the age of 2 years the mother noticed increasing swelling of the lower face. She has the same palpable nodules (lymph nodes) over the mandible as her brother (Case I). Dentition is so far normal. Skull X-ray (2.11.57) shows the characteristic picture of "fibrous dysplasia" of both jaws (Fig. 4). Clinically she might pass as a normal girl were the family history not known. There is the beginning of upward-looking eyes (Fig. 5).

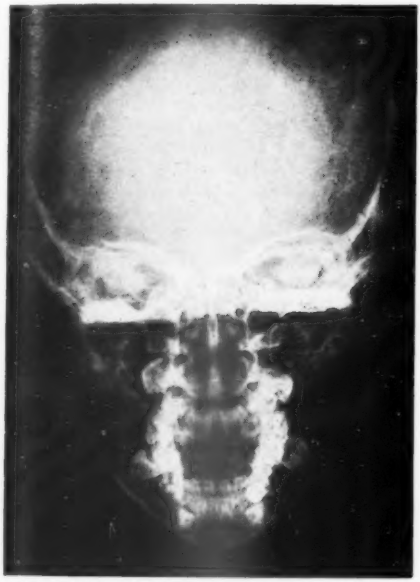


FIG. 4 (*Case II*) (antero-posterior).—Shows fibrous dysplasia of both jaws.



FIG. 5 (*Case II*).—Shows fullness of lower half of face; the eyes appear normal.



FIG. 6 (*Case III*).—Semi side of face shows fullness of lower half of face and eyes normal.



FIG. 7 (*Case III*) (antero-posterior).—Shows fibrous dysplasia of both jaws.

*Case III.*—J. K., male, aged 3 years (Mr. W. H. Maitland Smith's case). Was noted to have an enlarging face at age of 2 years 3 months. He has the typical swelling of the lower face, but eyes are not upward-looking (Fig. 6). X-rays of his jaws show loss of teeth and typical fibrous dysplasia (Fig. 7). He is entirely normal and well in all other respects. The grandmother was operated on for a swelling of the face when she was 17 years old.

*Discussion.*—Case I demonstrates the progress of an established case. Although there is the disability of indistinct speech, it is not at present proposed to operate to remove the excessive soft bone. Case II is in an early stage but it is possible, if it be accepted that the mother had this condition herself in childhood, that the child will not have so severe a deformity as her brother. She may be developing the characteristic appearance of the eyes. Case III, who is well established as regards jaw changes, has definitely normal eyes. The peculiar appearance of the eyes, together with fullness of the face, has led to the use of the name "cherubism". There is some attempt to give up this name and substitute the more general title of "fibrous dysplasia of the jaws". In the author's opinion this would be a pity as the name is a suggestive one and therefore clinically useful.

**Malignant Hæmangioendotheliomata Simulating Miliary Tuberculosis and Neuroblastoma of the Adrenal.**—JOHN LORBER, M.D., M.R.C.P., and A. G. ACKERLEY, F.R.C.S.

Girl aged 3 years, the only child of healthy parents.

1.6.57: She developed painless hæmaturia which became of increasing severity in the next few days. Ten days later she had severe abdominal pain and the hæmaturia continued. A radiograph of the abdomen was reported as negative. On cystoscopy blood was seen to come from the left ureter. An intravenous pyelogram showed dilated calyces on the left side. Whilst carrying out these pyelograms miliary opacities were observed in the lung fields. The presence of densely scattered miliary opacities in the lungs was confirmed on radiograph of the chest, but intradermal tuberculin tests were negative up to a dilution of 1/100 (Mantoux). She was afebrile and her C.S.F. was normal. It was felt wise to treat the child with 0·5 gram of streptomycin and 200 mg. isoniazid daily.

In the course of the next six weeks her condition deteriorated and she became anæmic.

No tubercle bacilli could be found at any time from the urine, from gastric washings or from sputum. The miliary shadows on radiographs of the chest became coarser.

In view of the negative tuberculin test, the absence of bacteriological confirmation and the failure to respond to antituberculous treatment the diagnosis of miliary tuberculosis was now in doubt and among other possibilities a neoplastic left kidney with secondary deposits in the lungs was considered.

14.8.57: She was transferred to the Department of Child Health, Sheffield. On admission, she was very pale (Hb 52%); her liver was enlarged to 4 fingerbreadths below the costal margin, but appeared smooth and was not tender. She had two very dark subcutaneous nodules just below the right scapula. There were no choroidal tubercles. On review of the earlier radiographs it was noticed that there was a patch of irregular calcification in the region of the left adrenal which was distinct from the miliary lesions in the lungs visible in the near vicinity. In addition, the left renal shadow as shown on the pyelogram was thought to be rotated and pushed away from the mid-line. In view of these additional findings a provisional diagnosis of neuroblastoma of the left adrenal was made and the miliary shadows in the lungs, the enlargement of the liver, the hæmaturia and the subcutaneous nodules were thought to be due to secondary deposits. The skin lesions were removed for histological study but were not diagnostic. The bone marrow was examined for evidence of neuroblastoma or other malignant cells and before the results of these investigations were known treatment was begun by intramuscular injections of 2 mg. vitamin $B_{12}$ daily for seven days and followed by the same dose on alternate days (130 mg./kg.). She was also given supportive transfusions. Investigations relating to tuberculosis were repeated, all with negative results, including tuberculin test with concurrent intradermal injection of cortisone (Citron and Scadding, 1957). The result of the bone-marrow examination was negative.

24.8.57: She had a succession of major convulsions. The C.S.F. after this episode was uniformly blood stained and all the changes in it could be attributed to intracranial hæmorrhage (R.B.C. 9,500, W.B.C. 600, protein 320 mg.%, sugar 62 mg.%). It appeared that she now had secondary deposits in the brain.

As no histological diagnosis was yet available, it was decided to perform a laparotomy (Mr. R. B. Zachary) on 28.8.57. The liver was found to be enormously enlarged and was studded with deep red-coloured tumours. A piece was removed for section.

The kidneys could not be seen, but a mass was felt in front of and above the left kidney.

Following this she generally became weaker and died on 10.9.57.

*Necropsy.*—A mottled vascular and grey mass approximately 4 cm. diameter was present at the upper pole of the left kidney. It was adherent to the spleen, infiltrated the diaphragm



FIG. 1.

and extended through the kidney substance to the renal pelvis which was surrounded by hæmorrhage. The left adrenal was not identified, but calcification was palpable in this region of the tumour. This was confirmed by a post-mortem radiograph (Fig. 1). The right kidney and adrenal showed several small, deep red, cystic nodules. Each ovary was slightly enlarged and contained central bluish-red hæmorrhagic tissue, but had an intact capsule. The liver (Fig. 2) was grossly enlarged without cirrhosis, and contained very many discrete red areas (0·2–2·5 cm. diam.), the largest with visible vascular spaces. Scattered red nodules were present on the peritoneal aspect of the intestine and in the marrow of the lower lumbar vertebral bodies. The lungs were studded thoughout with a multitude of small hæmorrhagic nodules (0·1–1·0 cm. diam.), some having brown centres.

The leptomeninges and brain contained red lobulated blood-filled nodules. The left occipital pole was congested and hæmorrhagic. Recent ante-mortem thrombus was present in the superior longitudinal and left lateral sinuses. Other organs showed no obvious abnormality.

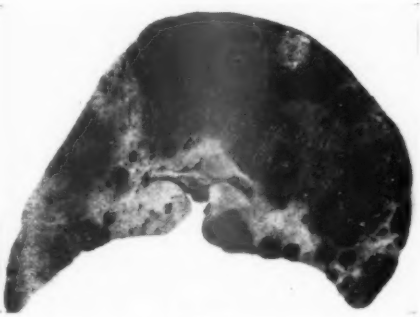


FIG. 2.

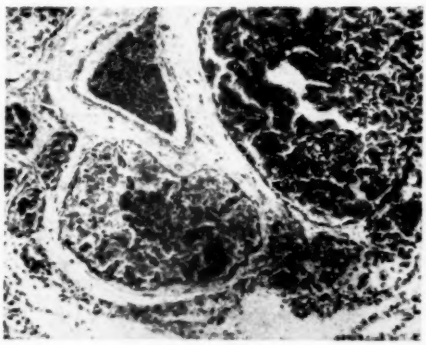


FIG. 3.—×79.

*Histology.*—A cavernous architecture is characteristic of the nodules in all the sites (Fig. 3). The tumour is formed of vascular spaces, many filled with blood, lined by endothelial cells which are flattened where the lining is one cell thick, but in many areas the cells are proliferating into the vascular spaces. Here they form rounded masses of cells of a more ovoid or polygonal shape. Mitoses are frequent.

In addition, and especially in parts of the mass near the apex of the left kidney, there are areas which show a more cellular pattern with finer vascular spaces, lined and separated by proliferating tumour cells (Fig. 4). Each nodule shows no surrounding fibrosis and infiltration outwards by the tumour cells is not a feature, but extensions of the vascular spaces insinuate between the constituent elements of the adjacent host parenchyma in the liver and kidneys. Tumour emboli in small vessels are seen in the sections of the lung (Fig. 5): the pathological appearances explain the radiological miliary mottling.

Hæmopoiesis is nowhere recognised: necrosis is present principally in the mass in association with the left kidney. This mass also shows calcification and fibrosis.

*Comment.*—This case was clinically remarkable for three reasons. First because radiologically the condition very closely imitated miliary tuberculosis. Secondly, when the

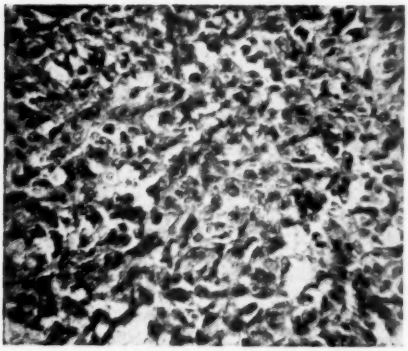


FIG. 4.—×198.

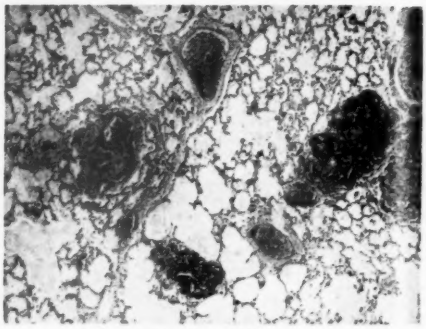


FIG. 5.—×30.

diagnosis of miliary tuberculosis became untenable, the calcification in the region of the adrenal suggested the probability of a neuroblastoma with secondary deposits elsewhere. Finally, histological evidence failed to confirm the second clinical diagnosis and replaced it with the diagnosis of a very rare condition.

The histological appearances demonstrated the vasoformative nature of this tumour whose proliferating cells are those lining the vascular spaces. It is therefore best called "hæmangio-endothelioma." Stout (1943) discussed this group of tumours. They are unusual and in the viscera have been most commonly described in the liver, especially in infants (Crocker and Cleland, 1957; Edmundson, 1956; Vidabaek, 1946) and may be found in the spleen (De Navasquez, 1936; Wright, 1949).

The present tumour is malignant and there is in addition evidence of terminal dissemination (Fig. 5). Vascular tumours are frequently multifocal and such a multiple origin is not excluded in this case. However, the appearance of the lesion in the region of the left adrenal suggests that it is of longer duration than those elsewhere. It is of interest that Menon and Annamalai (1934) described a hæmangioblastoma of the adrenal gland, and that in the case of a 4-months-old infant with a malignant hæmangioma of the lung (Wollstein, 1931) the adrenal was the site of a similar tumour.

REFERENCES

CITRON, K. M., and SCADDING, J. G. (1957) *Quart. J. Med.*, **26**, (N.S.), 277.
CROCKER, D. W., and CLELAND, R. S. (1957) *Pediatrics, Springfield*, **19**, 596.
DE NAVASQUEZ, S. (1936) *J. Path. Bact.*, **42**, 651.
EDMUNDSON, H. A. (1956) *Amer. J. Dis. Child.*, **91**, 168.
MENON, T. B., and ANNAMALAI, D. R. (1934) *J. Path. Bact.*, **39**, 591.
STOUT, A. P. (1943) *Ann. Surg.*, **118**, 445.
VIDABAEK, A. (1946) *Acta pædiat. Stockh.*, **33**, 129.
WOLLSTEIN, M. (1931) *Arch. Path.*, **12**, 562.
WRIGHT, M. (1949) *Arch. Path.*, **47**, 180.

**Neonatal Thrombocytopenic Purpura with Hæmangiomata.**—JEAN M. SMELLIE, M.A., B.M., M.R.C.P., D.C.H. (for B. E. SCHLESINGER, O.B.E., M.D., F.R.C.P.)

*History.*—A male infant admitted to University College Hospital Premature Baby Unit, aged 10 hours, following a normal delivery at home at 38 weeks.

Birth weight 4 lb. 4 oz. "Rash" noted at birth.

Mother aged 36, para–3. Normal pregnancy, except for pyelitis at 18 weeks and an I.V.P. at 20 weeks. No treatment given. No purpura during or before pregnancy. Spleen not palpable one week post partum.

*On examination aged 10 hours.*—Profuse purpuric rash varying in size from petechiæ to 1 cm. diameter, distributed over face > trunk > limbs. Few petechiæ in mouth. Spleen tip palpable. Liver 1 fingerbreadth. (*See* Fig. 1.)

*Investigations.—Infant aged 10 hours:* Hb 110%; platelets 23,000; bleeding time > 13 min.; clotting time normal. W.B.C. 16,500 (polys. 80%, lymphos. 15%, monos. 4%, eosinos. 1%); normoblasts 36/100 W.B.C. Direct Coombs' negative. W.R. and Kahn negative.

*Aged 6 days:* Marrow (R. tibial aspiration): No megakaryocytes seen in four smears, otherwise morphologically normal (Dr. E. M. Graves).

*Mother 7th day post partum:* Hb 98%; platelets 300,000. W.R. negative. Rhesus positive. Direct Coombs' negative.

No platelet antibody estimations were made in mother or infant.



FIG. 1.—R. H., aged 6 days, showing purpura.

*Treatment and progress* (*see* Fig. 2).—Started at twelve hours with ACTH gel 10 units and continued daily for six days. Platelets remained low, hæmoglobin level fell and fresh petechiæ developed.

*6th day:* Changed to oral cortisone for two weeks, 20 mg. daily steadily reduced to 5 mg.

A transfusion of 70 ml. packed stored cells was required for anæmia on the ninth day of treatment. Platelets rose to normal levels (190,000 at three weeks). During a three-week period without treatment the hæmoglobin fell without obvious purpura or bleeding but rose after cortisone was re-commenced. Dosage was reduced gradually from 20 mg. to 2·5 mg. daily and this maintenance dose was continued until seven months. Ferrous gluconate 100 mg. b.d. was given until fifteen months.

*Subsequent progress.*—Spleen palpable until 7 months. Platelets normal from 3 weeks. Marrow smears from iliac crest aspiration showed:

2 weeks —No megakaryocytes.

While on cortisone (2½ weeks to 5 months):

2½ weeks —1 atypical megakaryocyte.
2 months } Very occasional mature
5 months } megakaryocytes.
11 months —No megakaryocytes.

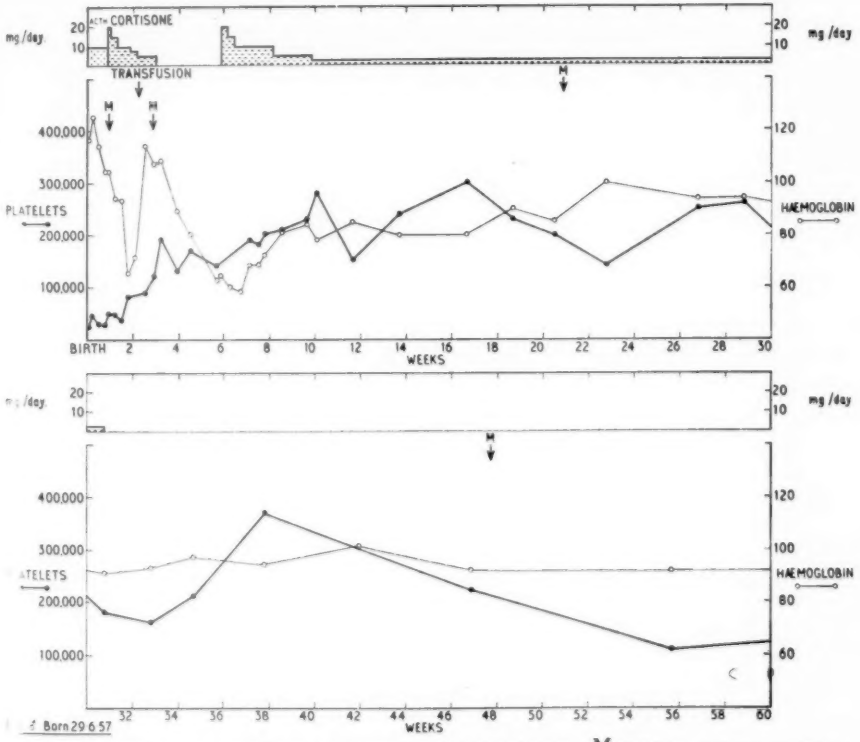



FIG. 2.—Platelets/c.mm. and Hb % (14·8 grams = 100% Haldane). M ↓ indicates marrow puncture.

Hæmangiomata of the raised capillary or strawberry nævus type first noted at five to six weeks. Distributed mainly right side of body, right upper arm, chest, thigh, knee and lower eyelid; the last was treated with carbon dioxide snow (Dr. P. J. Hare). Fresh hæmangiomata developed until eleven months when he had a total of ten.

Pertussis 16 months. Otitis media 11, 13 and 14 months. Milestones: normal physical and mental development.

*Comment.*—The main features of interest are: the occurrence of thrombocytopenia in an infant where the mother was normal; the persistent deficiency of megakaryocytes in marrow smears; and the association of hæmangiomata with thrombocytopenia.

Considering the ætiology and mechanism of the purpura, Stefanini and Damashek (1955), Robson and Walker (1951) and others have divided cases into those born to mothers with idiopathic or secondary thrombocytopenic purpura and those born to normal mothers.

Where the mother had idiopathic thrombocytopenic purpura with or without a previous splenectomy, platelet antibodies have been demonstrated in most cases in which these have been investigated (Harrington *et al.*, 1953).

Where the mother was normal, the possible mechanisms were:

(1) Congenital hypoplasia of marrow of the Fanconi type.

(2) Congenital aplasia of megakaryocytes.

(3) Mother-baby anti-platelet antibody mechanism, analogous to hæmolytic disease.

In this case, the marrow showed no general hypoplasia or evidence of leukæmia.

In the true amegakaryocytic types as described by Bell *et al.* (1956), Emery *et al.* (1957), and Greenwald and Sherman (1929) the outcome was fatal, there being no response to cortisone or splenectomy where this was tried and there were other congenital malformations.

Lastly there was the possibility of the production of anti-platelet iso-antibodies in the mother (Schoen *et al.*, 1956; Harrington *et al.*, 1953; Tullis, 1956).

Against this was the absence of megakaryocytes in the marrow. A normal or increased number of megakaryocytes would be expected as this occurs in idiopathic thrombocytopenic purpura in children or adults.

In the literature, however, there are few marrow studies reported in patients in whom platelet antibodies have been demonstrated and the reverse is also the case; where the marrow has been examined, antibodies have not been estimated. However, in at least two reported cases of neonatal purpura occurring in infants of mothers with idiopathic thrombocytopenic purpura when this is presumed, but not proved, to be an immune mechanism, the marrow has been found deficient in megakaryocytes at post-mortem (Whitney and Barritt, 1942; Finn, 1944).

In favour we have the brief period of purpura (which might have been self-limited as is the common course if untreated) and the apparent response to cortisone in the child of a multiparous mother. Although megakaryocytes were still sparse or absent in marrow smears at 11 months the circulating platelets remained normal in number from 3 weeks and the megakaryocytes may have been producing them, possibly in the liver.

It was unfortunate that we were unable to estimate the anti-platelet antibodies at the time of admission, as this alone would provide the answer.

Lastly, the association of thrombocytopenia with hæmangiomata may be incidental, but is well documented. In most of the reported cases, hæmangiomata have preceded the purpura and no improvement in thrombocytopenia has occurred from splenectomy or cortisone until the hæmangiomata have regressed spontaneously or following therapy (Huysinga and Minder, 1957; Silver *et al.*, 1948; Meeks *et al.*, 1955).

## REFERENCES


Bell, A. D., Mold, J. W., Oliver, R. A. M., and Shaw, S. (1956) *Brit. med. J.*, ii, 692.

Emery, J. L., Gordon, R. R., Rendle-Short, J., Varadi, S., and Warrack, A. J. N. (1957) *Blood*, **12**, 567.

Finn, W. F. (1944) *Amer. J. Obstet. Gynec.*, **48**, 497.

Greenwald, H. M., and Sherman, I. (1929) *Amer. J. Dis. Child.*, **38**, 1245.

Harrington, W. J., Sprague, C. C., Minnick, V., Moore, C. V., Aulvin, R. C., and Dubach, R. (1953) *Ann. intern. Med.*, **38**, 433.

Huysinga, J. K., and Minder, W. H. (1957) *Arch. Chirurg. Neerland*, **9**, 193.

Meeks, E. A., Jay, J. B., and Heaton, L. D. (1955) *Amer. J. Dis. Child.*, **90**, 349.

Robson, H. N., and Walker, C. H. M. (1951) *Arch. Dis. Childh.*, **26**, 175.

Schoen, E. J., King, A. L., and Douane, R. T. (1956) *Pediatrics, Springfield*, **17**, 72.

Silver, H. K., Aggeler, P. M., and Crane, J. T. (1948) *Amer. J. Dis. Child.*, **76**, 512.

Stefanini, M., and Damashek, W. (1955) The Hæmorrhagic Disorders. New York.

Tullis, J. L. (1956) *New Engl. J. Med.*, **225**, 541.

Whitney, L. H., and Barritt, A. S. (1942) *Amer. J. Dis. Child.*, **64**, 705.

**Thyrotoxicosis in a Mongol.**—J. H. DIGGLE, M.B., M.R.C.P., and R. S. WEETCH, M.B., M.R.C.P. (for T. COLVER, M.D.).

J. A., female, born 30.4.49. First seen at 1 month old with the usual signs of mongolism. The heart is normal. She first walked at 3½ years and showed marked mental retardation.

*History.*—At 6 years of age she began to lose weight and over the following seven months she developed exophthalmos and thyroid enlargement and became very excitable and was restless at night. There was little sweating but she always felt hot to the touch. Later there was polyuria and diarrhœa.

*On examination.*—Height 44¼ in. (within normal range; female mongols are often 4 to 8 in. short of the lowest 5 percentile). Weight 33 lb. (well below the 5 percentile).

The thyroid was soft and diffusely enlarged with a systolic thrill over it. Pronounced proptosis present with lid retraction, more marked in the left eye than the right (Fig. 1). Heart-rate 150 per min. Sleeping pulse 125 per min. average. Blood pressure 130/60. The heart was overacting and slightly enlarged on X-ray. No cardiac murmur was heard. No tremor of the hands was seen but there were jerky movements like chorea. Temperamentally she was sensitive and emotionally labile. Much more animated than most mongols: hyperkinetic at times.



FIG. 1.

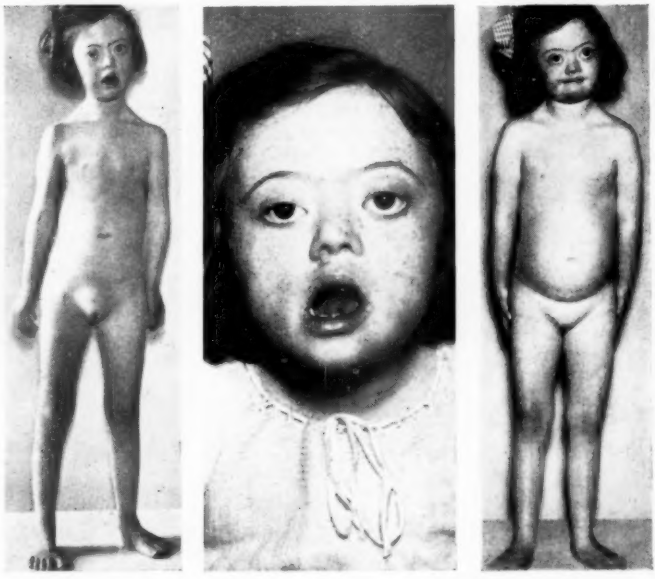


FIG. 2.

*Investigations.*—Bone age probably 10 years, i.e. all carpal centres were present, including the pisiform. X-ray of skull showed a normal pituitary fossa.

Serum cholesterol 130 mg. %. Total serum lipoids 275 mg. %. B.M.R. was not attempted on account of her low I.Q.

$$\text{Ratio of } \frac{\text{Creatine}}{\text{Total creatine + creatinine}} \text{ was } 15{\cdot}6\% \text{ (normal).}$$

Radio-active iodine studies: 5$\mu$c. of $^{131}$I given

(1) Thyroid gland uptake:
- After one hour 56% of dose given.
- After four hours 84% of dose given.
- After forty-eight hours 74% of dose given.

(2) Blood concentration of $^{131}$I: The conversion ratio =

$$\frac{\text{Protein-bound iodine} \times 100}{\text{Total plasma activity}} = 83{\cdot}7\%.$$

In spite of a possible total error of 13% due to technical factors these figures show unequivocal evidence of well-marked thyrotoxicosis.

A therapeutic trial with Lugol's iodine subsequently produced a fall of 20 per min. in the average pulse rate and during four weeks on potassium iodide the patient gained 6½ lb. and became quiet and much less active. The pulse pressure fell from 70 mm. to 35 mm.Hg.

*Treatment.*—Carbimazole 15 mg. per day was given for four weeks, then the dose was gradually reduced to 7½ mg. per day. She lost all signs of hyperthyroidism and became slower, rather obese and much easier to manage at home. The exophthalmos has almost disappeared and the thyroid gland is now small and firm (Fig. 2).

Since the thyrotoxicosis has been controlled the 17-ketosteroid excretion has been estimated at 1·1 mg. in twenty-four hours, which is the upper limit of normal at this age. Ketogenic steroids were 5·0 mg. in twenty-four hours.

*Comment.*—Gilchrist (1946, *Brit. med. J.*, i, 237) described a female mongol aged 22 with thyrotoxicosis and McGirr and Murray (1956, *J. clin. Endocrin.*, **16**, 1) reported a case in a female mongol of 23.

Thyrotoxicosis is very uncommon in young children and it is the great rarity of its combination with mongolism which prompts us to present this paper.

We wish to acknowledge the help received from Dr. Harold Miller (Physicist) who carried out the radio-iodine measurements.

**Symptomless Hypoplasia of One Thenar Eminence in Childhood—The Presenting Feature of a Bizarre Developmental Syndrome** (Two Cases).—TREVOR P. MANN, M.D.

*Case I.*—P. H., born 3.2.49. (Shown November 23, 1956, aged 7½ years.)

*History.*—Referred to hospital with "wasting" right thenar eminence, first observed in infancy, and asymmetrical head posture simulating torticollis. A healthy child. Right-handed. No paræsthesiæ or other subjective symptoms affecting hands.

*On examination.*—Position of shoulders asymmetrical—right lower than left. Head slightly deviated towards right shoulder (Fig. 1). Upper dorsal kyphosis. Marked "wasting" right thenar eminence—scooped out appearance (Fig. 2). Interossei normal.



FIG. 1 (*Case I*).—Head deviated to right. Drooping of right shoulder.



FIG. 2 (*Case I*).—Hypoplasia of right thenar eminence.

No muscle tenderness. Sensation hands intact. C.N.S. normal. Slight weakness of opposition and thumb abduction movements right hand. Right thumb and nail definitely smaller than left thumb and its nail. Brachial pulses equally palpable; brachial blood pressure equal on two sides. Absent right radial pulse—not palpable after immersion in a hot bath. Right ulnar pulse palpable. Left radial and ulnar pulses normally palpable.

*X-ray examination* (Dr. J. Rubin).—Cervical spine normal. Transverse processes C.V.7 prominent but not abnormally so. No cervical ribs. Dorsal spine: no evidence of scoliosis. Hands: Delayed development of right lateral carpal bones. No ossification is yet evident in right scaphoid and its centre usually appears by 5 years (usual limits 3 to 8 years). The trapezium is much smaller on the right side. There is a little atrophy of the first metacarpal bone, its shaft being definitely thinner and its cortex slightly thicker than the corresponding left bone. Its proximal epiphysis is slightly smaller and rounder than the left epiphysis which is more oval in shape. The thumb phalanges are also very slightly smaller on the right (Fig. 3).




FIG. 3 (*Case I*).—Delayed development of right lateral carpal bones. Narrowing of shaft of first right metacarpal bone.




FIG. 4 (*Case II*).—Delayed development of right lateral carpal bones. Narrowing of shaft of first right metacarpal bone.

*Case II.*—C. P., born 13.10.50. (Shown November 22, 1957.)

*History.*—December 1956 attended hospital with injury to right wrist following a fall. "Wasting" of right thenar eminence noted by the casualty doctor. This had not previously been observed by the parents. A perfectly healthy child. Left-handed. No paræsthesiæ affecting arms or other symptoms such as circulatory and temperature changes.

*On examination.*—Physical signs essentially the same as those given above for Case I and summarized below:

*X-ray examination* (Dr. J. Rubin).—Cervical spine normal. No cervical ribs. There is a pseudo-arthrosis of the first and second right ribs. There is a definite difference in the development of the hands and wrists—the right being retarded in comparison with the left (Fig. 4). Thus there is an obvious difference between the two scaphoids, the maturation on the right side lagging about one year behind the left. Also the right trapezium and trapezoid

similarly show retarded development. The distal epiphysis of the right ulna consists of two small ossific centres whereas a well-defined bony centre is evident on the left. The first right metacarpal shaft is thinner than the left and its cortex thicker on the medial aspect. Its proximal epiphysis is slightly smaller and more rounded than the corresponding left epiphysis which is more oval in shape. Comparison of thumb phalanges on the two sides shows the right ones to be slightly smaller.

The syndrome exhibited by these 2 children consists of the following components:

(1) Hypoplasia of one thenar eminence and, to a lesser degree, of the related thumb.

(2) Absence of the radial pulse on the affected side.

(3) Drooping of the shoulder on the abnormal side.

(4) X-ray changes in the thumb bones and wrist of the abnormal limb which in essence are: (*a*) Delayed development of the lateral carpus, retardation being especially conspicuous in the scaphoid bone. (*b*) Narrowing of the shaft of the affected first metacarpal bone, the proximal epiphysis of the latter being smaller and more rounded in shape. (*c*) Hypoplasia of the thumb phalanges.

Hanley and Conlon (1957, *J. Bone Jt. Surg.*, **39B,** 458) have described a syndrome in two adults resembling the one reported here. Their Case 1, in particular, appears to be suffering from a very similar disturbance. It is difficult to assess their second case as the clinical account is incomplete. The affection was bilateral in these adults and in both there was an associated proximal bony abnormality as in Case II here (a large cervical rib in one and a spina bifida of the first thoracic vertebra in the other).

This syndrome, presumably congenital in origin, must be considered in the differential diagnosis of "wasting" of the intrinsic thumb muscles in children and adults. It does not appear possible to relate, in embryological terms, the various anatomically associated tissue defects.

I am indebted to Dr. Eva Frommer for drawing my attention to Case II.

**Tropical Eosinophilia.**—C. W. KESSON, M.D.

M. C., male, aged 11 years. Cingalese, born in Ceylon but moved to Singapore at 1 year of age and to the U.K. in May 1956.

*Family history.*—Parents well with normal white blood counts and negative W.R. and Kahn reactions. Maternal great-uncle treated for tropical eosinophilia in Singapore 1953. Another maternal great-uncle and a great-grandmother suffered from asthma.

*Previous illnesses.*—Treated for roundworms 1949. Tonsils and adenoids removed 1954.

*Present illness.*—Fever and purulent nasal discharge began in December 1956, and progressed to cough, wheeziness and severe dyspnœa. The illness lasted two weeks but some cough persisted and he remained short of breath on exertion. Exacerbations occurred every four to six weeks and in April 1957 he was referred to Victoria Hospital for Children, two weeks after an episode. At that time there was no evidence of respiratory infection. Spleen palpable, W.B.C. 20,000, 61% eosinophils.

He was admitted later in a typical asthmatic attack. His temperature was 99° F. He had a mild upper respiratory tract infection. There was marked bronchospasm and generalized expiratory rhonchi. The edge of the spleen was 1 in. below the costal margin.

*Progress.*—The asthmatic attack subsided with aminophylline and phenobarbitone though a cough with some coarse scattered rhonchi persisted. Repeated stool examination failed to reveal ascaris ova but a course of hexylresorcinol was given. No worms were passed. On 10.6.57 he developed a temperature of 101° F. with faucial infection and an asthmatic attack. Next day a week's course of oral Stovarsol was instituted and injections of penicillin for the streptococcal throat infection. The temperature remained raised till 22.6.57 when his general condition began to improve. He was discharged well on 2.7.57. The spleen remained enlarged. W.B.C. 18,000, 43% eosinophil cells.

He has remained well and free of asthma. W.B.C. now 8,800 with 10% eosinophils.

*Investigations.*—Chest X-ray: increased vascularity of lung fields. Mantoux 1 : 1,000 negative. Sputum: pus cells predominated. Fæces and urine: N.A.D. Blood: protein 7·2 g./100 ml. Marked increase in $\gamma$ globulin. W.R. and Kahn positive on 24.5.57 and 31.5.57. Treponemal W.R., standard W.R., and Price's precipitation reaction negative on 13.6.57. W.R. and Kahn negative on 24.9.57. Films showed no malaria or microfilaria.

Skin tests: pollens, Casoni, histoplasmin, coccidiosis negative. Filaria positive.

The following cases were also shown:

**Cushing's Syndrome.**—Dr. E. GOLDBLATT (for Dr. A. P. NORMAN).

**Aldosteronism in Infancy.**—Dr. J. W. PLATT (for Dr. B. E. SCHLESINGER).

**Hepatomegaly ? Cause. Failure to Thrive.**—Dr. LESLIE SCOTT.

**Meningococcal Septicæmia and Early Meningitis.**—Dr. M. PEARD (for Dr. URSULA JAMES).

# Section of Psychiatry

President—Professor E. STENGEL, M.D., M.R.C.P.

[*January* 14, 1958]

## DISCUSSION ON THE LEGAL ASPECTS OF SUICIDAL ACTS

**Dr. Doris Odlum** (Bournemouth):

Suicide is a felony. It is a common law offence and regarded as a form of homicide. The origins of this law are lost in antiquity, but there are records relating to it dating from mediæval times. The original penalties were burial at a cross roads with a stake through the heart and forfeiture of goods to the Crown. As the result of pressure of public opinion this form of burial was discontinued from 1824 but suicides had to be buried between 9 and 12 at night without any ceremonial in unconsecrated ground. This was not repealed until the 1880s. The confiscation of goods was discontinued from 1870. In spite, however, of the removal of all sanctions, suicide still remains a felony in law. This has given rise to the custom of coroners giving a verdict that the balance of mind was disturbed in a large number of cases. From the point of view of the relatives and friends it is doubtful whether it is less distressing to have to face a verdict of felony or mental derangement. Attempted suicide, because it is an attempt to commit a felony, is itself an indictable offence and comes under the category of a misdemeanour. A conviction therefore carries the stigma of a criminal record. It is described in legal language as "unlawfully attempting to commit suicide against the peace of our sovereign lady, the Queen, her crown and dignity". Cases formerly had to be tried at quarter sessions or assizes. By the Magistrates' Acts of 1935 to 1951 they can now be tried before a Magistrate's court with the consent of the accused. The maximum penalty that a Magistrate's court can inflict is six months' imprisonment but if tried at Assizes or Quarter Sessions heavier penalties can be inflicted and a sentence of two years' imprisonment was recently given. (This, however, was reduced on appeal by Lord Justice Goddard to two months' imprisonment.) The criminal statistics for the years from 1946 to 1955 show that the total number of cases of attempted suicide known to the police were 44,956. Of these, 5,794 were brought before the courts and subjected to trial. 5,447 were found guilty and thus stigmatized as convicted criminals. 308 were sentenced to terms of imprisonment without option of a fine. The numbers of men sentenced to prison were slightly higher than those of women. Thus an average of over 13 people in a 100 were prosecuted and practically all were convicted. It is therefore obvious that the legal attitude to attempted suicide is still largely mediæval. It has been claimed that attempted suicides are only brought to court for their own protection, but evidence is available that this is by no means always the case.

In 1947 a joint committee of doctors and magistrates sponsored by the British Medical Association published a report entitled "Attempted Suicide, the need for an alteration in the Law". This report was endorsed by the medical members of the committee and accepted by the Council of the B.M.A., but at the time no further action was taken. In July 1956 the Representative Body of the British Medical Association passed a resolution deploring the fact that during recent years a considerable number of people had been imprisoned for attempting suicide and supporting the conclusion of the 1947 report that there was a strong case for amendment of the law so that attempted suicide would not be dealt with as a legal offence and suggesting that the committee should give further consideration to the matter and also to the treatment of attempted suicides, having regard to the fact that the majority were in need of psychiatric treatment. The joint committee have, during the past eighteen months, been considering the whole question. They have taken evidence from a number of consultants in general hospitals who have stated that they find no difficulty in dealing with

attempted suicides from the medical and social point of view without invoking legal intervention. The committee has considered the report of Dr. Epps on 100 women in prison on attempted suicide charges. It has also received oral evidence from Professor E. Stengel, Professor of Psychiatry at Sheffield University, and discussed his paper on "Society and Suicide". It has considered a report on the subject which has been accepted by the Council of the Medical Women's Federation which considered that the present law required amending. It has received information about the law and practice in other countries. With the exception of India and some of the American states there is no country which regards attempted suicide as an offence in law. It has received evidence from Austria, France and other countries where there is no legal intervention that they do not appear to find any difficulty in dealing with cases of attempted suicide. In Scotland attempted suicide is in the large majority of cases dealt with as a medical matter but in the very few cases where there are no relatives or friends available and where the individual is entirely unco-operative, it is dealt with as a breach of the peace in the interests of the person who has made the attempt and/or the community. No evidence has been found to support the claim that the fact that attempted suicide is a crime acts as a deterrent nor that the attempted suicide derives any benefit from being brought to trial, convicted, remanded as a convicted criminal to a prison hospital for investigation, or imprisoned. There is, on the contrary, much evidence that this greatly adds to the distress both of the person who has attempted suicide and of his family and friends. Cases where, after conviction, the attempted suicide is put on probation on condition that he accepts psychiatric treatment could be much better dealt with by the medical and social agencies available without the intervention of the law.

It would appear that in the large majority of cases there is no good reason for legal intervention at all. In the few who will not co-operate and who have no friends or relatives who are prepared to take care of them the difficulty could be met by making the breach of the peace procedure applicable in England and Wales to those who require care and protection for their own safety or in the interests of the community.

The question has been raised as to the position in regard to life assurance policies. Information has been obtained from the leading insurance companies to the effect that if a person has paid one year's premium the policy would be fully honoured in the case of suicide regardless of the coroner's verdict. No policy would be determined because the holder had attempted suicide. Therefore the legal position does not affect the insurance issue either way.

A criminal record, however, could prejudice the possibility of obtaining an emigration permit or of obtaining certain posts either in this country or overseas. The question has also been raised whether the doctor has a duty to report a case of attempted suicide to the police. Advice has been taken on this point and it would appear that there is no obligation on any citizen to report a misdemeanour. He would, however, have an obligation to report a case of accomplished suicide as this is a felony.

It would appear that the only possible reason for continuing to regard either suicide or attempted suicide as a criminal offence would be the concept that suicide is a form of murder and therefore should be punished from a retributive point of view or as a possible deterrent. It has already been pointed out that there is no evidence that it does in fact act as a deterrent. The concept of purely retributive punishment is no longer acceptable to the majority of the community who take a more humane and constructive attitude.

**Dr. P. Epps** (London):

I propose to leave the more theoretical and historical aspects of the relation between the law and suicidal acts, and to concentrate on the practical side of this problem. During the three years 1954–1956, I interviewed a consecutive series of 100 women admitted to Holloway Prison Hospital on charges of attempted suicide. Those women who had additional charges such as larceny, fraud, &c., were excluded from this series, except in two cases where the other charge was not pursued.

All the 100 women (except one, who appeared at Sessions) came from Magistrates' courts in London and in those counties from which Holloway draws its population, i.e. the Home Counties, East Anglia and the South and East of England. The women fell into three categories: firstly, 51 were sent by the courts under Section 26 of the C.J. Act of 1948, which means they are convicted of the charge, but are sent from court into prison for one to three weeks for a medical report and recommendation, with which they then return to court; although they have the advantage of this report and recommendation, they suffer the disadvantages of a convicted person while in prison. Secondly, 43 were admitted on remand with a request for a medical report in 31 cases. Thirdly, 6 were admitted already sentenced,

the sentences varying from three to nine months' imprisonment. We can conclude that the courts are usually ready to seek medical advice, since in 82 of the 100 cases a medical report was requested from prison, and in some of the remaining 18 cases it may have been available from some other medical source.

Turning now to events occurring between the suicidal attempt and the first court appearance, the large majority, 75, had been treated in general hospitals. Of this 75, 30 had been kept in hospital for only a few hours for first-aid treatment, 23 spent up to three days, 15 from three to seven days, and 7 from one to two weeks. The 53 who spent three days or less in general hospitals were probably seen only by casualty officers or junior doctors, and one wonders if they were assessed on their physical rather than their psychiatric state. The 22 who were retained longer than three days and up to two weeks may have had the advantage of a psychiatrist's opinion and recommendation to the court. These general hospitals appeared, on the whole, to have been large ones, and in London 16 of the patients came from 8 teaching hospitals. Of the remaining 25, 15 were under psychiatric supervision, 9 in observation wards and 6 in mental hospitals, one of the latter being sent there by the court for a medical report. The remaining 10 went directly to a police station and thence to court, apparently because of the trivial harm sustained by the patient in the suicidal attempt.

The majority of these women, 64, had had no previous acquaintance with courts or prisons and a further 6 had only been acquainted through an earlier charge of attempted suicide. The remaining minority of 30 had previous convictions for larceny, drunkenness, &c. A total of 11 had previously been charged with attempting suicide, and of these 7 had been put on probation (2 on two occasions), 2 sentenced to imprisonment, 1 certified insane and 1 given an absolute discharge. Since these 11 reappeared on the same charge, it is doubtful whether these previous convictions had had any deterrent effect, and this opinion is reinforced by the fact that 42 of the 100 admitted that they knew that court proceedings could follow their suicidal acts.

The usual medical and social details were noted in taking each woman's history, and the group as a whole was not very different from those other groups collected in observation wards, such as Professor Stengel's group (1952) and Dr. Batchelor's group in Edinburgh Royal Infirmary (Batchelor and Napier, 1954). Ages varied from 17 to 81, 75% being under 40 years of age. Social isolation and unhappy homes were prominent; 44 were married, but of these 27 were separated or divorced, 10 claimed to be unhappily married and 2 had husbands in prison. Only 5 said their marriages were happy, and of these 2 were epileptic, and 2 psychotic; 8 were widowed and of the 48 single women, 12 were cohabiting or in unsatisfactory, involved situations.

Physically the group was a healthy one; only 2 women, one with asthma and 1 with tuberculosis, had any physical disability. But 49 gave a history of past mental illness, 42 having been in mental hospitals, 20 more than once. 10 had been certified, 27 had been voluntary patients, and 5 both certified and voluntary. 4 had had psychiatric out-patient treatment, 3 had been treated by their own doctors, and 2 had had leucotomy. 44 admitted to previous attempts at suicide; the rest seem to have been charged on their first attempt, which is not in line with the commonly held belief that the police never charge anyone on their first attempt.

This high incidence of past mental illness suggests that this is a mentally ill group, and this is confirmed by diagnosis. Of the 100 women, 49 were classed as neurotic, 19 as psychotic, 16 as psychopathic, 11 as epileptic and 5 as borderline or mental defectives. There were 24 chronic alcoholics in the group, 16 of whom attempted suicide after drinking. Of these 24 alcoholics, 10 were diagnosed as neurotic, 8 as psychopathic, 4 as psychotic, 1 as epileptic and 1 as a borderline defective.

Alcoholism was rather commoner in this prison group than in those two groups previously mentioned, and this may explain to some degree the short period for which some of these patients were retained in general hospitals after the attempt. Some patients can be a disturbing influence in a ward; this would mainly apply to alcoholics and some psychopaths, and in such cases a charge such as breach of the peace or drunkenness would meet the case. The abolition of "attempted suicide" as a charge would avoid the admission to prison of mentally ill patients, to whom such an experience may be an additional cause of depression and to whose relatives it can be a source of distress.

In the recommendations sent to court, 12 were recommended for certification, 11 as insane and 1 as mentally defective; 38 were referred for treatment as voluntary patients in mental hospitals, and the court included a probation order for 21 of them. 27 were placed on probation, of whom 21 were recommended for treatment at a psychiatric out-patient clinic. Half the group therefore was thought to be in need of in-patient treatment in mental hospitals, and a further 21 of out-patient psychiatric treatment. 7 were sent to a hostel or convent,

5 of them on probation. The total put on probation by the court was 53, more than half. 6 were discharged by the court.

The remaining 10 were sentenced to imprisonment, varying from two to nine months. 3 appealed, all successfully, against their sentences, 2 being placed on probation and the third being treated as a voluntary patient. 1 was certified as an alcoholic psychotic during her sentence and 6 completed their sentences. It is difficult to see why these particular 10 were sentenced; 6 came from courts in the provinces, and 4 from London; 3 had had numerous previous convictions, 4 had had none, while the 3 who appealed had each had 1 previous conviction. 4 were psychopaths, 3 neurotics, 1 of whom was alcoholic, 1 was epileptic and 1 a borderline mental defective. No definite sentencing policy is discernible, but possibly it is too small a number to allow conclusions to be drawn.

With reference to charges of attempted suicide admitted to men's prisons, Sir Norwood East (1913) published a paper on 1,000 cases admitted to Brixton Prison in the previous three and three-quarter years. This suggests that there was an approximate yearly intake of some 250 men on this charge. Dr. J. C. McI. Matheson, recently Principal Medical Officer at Brixton Prison, tells me that in 1955, 44 men were admitted on this charge, showing a considerable decrease in comparison with Sir Norwood East's figure, for which the increase in psychiatric services in the country would seem to be one of the main reasons.

The annual criminal statistics for England and Wales show that some 4,000 to 5,000 attempted suicides are known to the police each year, the figure having a tendency to rise over the past ten years, so that it stood at 5,220 in 1955. Of these, the police usually charge about 1 in 8, so that proceedings were taken against some 600 (twice as many men as women) in Magistrate's courts in that year. It is generally thought that the main factor that accounts for a charge being made is the absence of any relative who will hold himself responsible for the safety of the person concerned in the attempt and the consequent fear of further suicidal attempts.

It would appear that this solution of the problem, arrived at between police and relatives, leaves out of the picture the psychiatric assessment and treatment, opportunities for which have increased so much with the growth of the psychiatric services both in mental and general hospitals, for in-patients and out-patients, in recent years. Not only is there increased facility for psychiatric treatment, but also there are more social agencies than in former years, particulars of which are better known to psychiatric and other social workers than to the police.

To return to the attempted suicides proceeded against in 1955, I should like to mention two of the methods for dealing with them, namely, probation and imprisonment. Probation appeared to be the most popular means of dealing with the prisoner, as it was in the case of the 100 women previously described, and accounted for 358, or more than half. Excellent though the supervision given by Probation Officers is, these patients mostly need psychiatric treatment and time and effort would probably be saved if the supervision was left to social workers in the mental health services.

In contrast to the large number put on probation, a prison sentence was given to 44, the sentences varying from two weeks to six months. It is not revealed how many appealed against their sentence, but all those who appealed among the women mentioned earlier were successful. This suggests that there is some doubt within the legal profession as to whether a prison sentence is suitable for this offence, and may even indicate an alignment of opinion between both lawyers and doctors that the man or woman who attempts suicide should not be regarded as a criminal.

Finally, to summarize these points already touched upon, which would appear important and perhaps controversial:

(1) The majority appear to spend so short a time in general hospitals between the suicidal act and the court appearance that it is doubtful if they have had anything more than an assessment of their physical state.

(2) The large majority have had no previous acquaintance with courts or prisons, and even though they remain in the prison hospital and not in the prison, such an experience is inadvisable in those already mentally ill.

(3) There is no evidence that any deterrent purpose is served by charging these patients.

(4) The use of probation for the majority of these cases shows a lack of economy in the use of the available social services.

(5) The growth of psychiatric services in this country over recent years defeats the argument that prison should be used as a place of safety for the potential suicide. Though suicide may generally be regarded as an undesirable or even as an anti-social act, we in this country are

in the minority in regarding it as a criminal act. Moreover, we are illogical in that those who fail in the attempt are treated as criminal, while those who succeed are usually found at the coroner's inquest to have been unbalanced in mind.

I am indebted to the Prison Commissioners for permission to give the details of the 100 women seen in prison, but any views expressed are my own and not necessarily those of the Prison Commissioners.

REFERENCES

BATCHELOR, I. R. C., and NAPIER, M. B. (1954) *J. Neurol. Psychiat.*, **17**, 261.
EAST, N. (1913) *J. ment. Sci.*, **59**, 428.
STENGEL, E. (1952) *Proc. R. Soc. Med.*, **45**, 613.

**Dr. I. R. C. Batchelor** (Liff, Dundee):

An attempt to commit suicide is not *per se* an offence in Scotland. The individual may be hurried to hospital by the police and no legal action taken; or he may be charged with a breach of the peace: it is exceptional for him to be brought before a court. There is no hard-and-fast procedure in Scotland, the practice varying in different parts of the country. The percentage of cases of attempted suicide reported to the police in Scotland is not accurately known; in one city hospital records suggest that perhaps one-half of the cases are not so reported.

When the suicidal individual is charged with a breach of the peace, most often the suicidal attempt has been made in public and proceedings are taken on the grounds that the attempt has been carried out in circumstances which tend to alarm the lieges and constitute a breach of public order. For example, a shop assistant, aged 20, was charged because she "did attempt to commit suicide by jumping from a balcony on the first flat of a tenement, to the ground below, a distance of approximately 20 feet and did thus commit a Breach of the Peace". Rarely, when the suicidal attempt has been made in the individual's home, if the police have been informed by neighbours or relatives, a charge of breach of the peace may be brought: but if it did come to court, one supposes that a charge of breach of the peace, originating in such private circumstances, would be difficult to sustain.

Though these charges are made, the cases practically never come to court. The suicidal individual is taken to a general hospital by ambulance for treatment, and a "detention slip" is forwarded to the superintendent of the hospital from the local police station. This "detention slip" informs the hospital superintendent that his patient is a prisoner charged with breach of the peace and directs him to inform the police authorities the date and hour on which it is proposed to discharge the prisoner, in order that arrangements may be made for taking him into custody. The accused may be interviewed in hospital by two detective-constables, in plain clothes, cautioned and charged with the offence as libelled. The police interrogate witnesses and relatives and report to the City Prosecutor the circumstances of the case, the events which had preceded the suicidal attempt, the apparent causes of it, the individual's mental state (if known) and his or her response to the charge. In this report it is usually also stated that the individual has been or will be examined by a psychiatrist and his mental treatment undertaken. That is as far as legal action goes. The Prosecutor informs the police that he does not intend to take further proceedings, the charge is abandoned, the "detention slip" is cancelled, and the case rests in medical hands. If the hospital doctors state that the suicidal individual is unfit to be interviewed and charged, the police readily accept this advice, and the police themselves may decide on seeing the person that he or she is too unwell to be cautioned and charged. In the case of young persons particularly, the police may offer help from a court social worker or probation officer.

This legal practice is, from the psychiatrist's point of view (to state a personal opinion), open to criticism but not to severe criticism. Although the interview of the patient in hospital by the police is brief, it does aggravate in many cases the patient's distress of mind: one must add that an instance cannot be recalled when it was seriously prejudicial or seemed to have lasting ill-effects. The police officers are helpful, sympathetic and considerate in their attitudes, but from a medical point of view their visits are an intrusion, and tend to delay healing processes. Furthermore, to bring a charge when there is little or no intention of proceeding with it, seems sterile. Sometimes a suicidal individual will want to leave hospital as soon as he has regained consciousness or had his wounds dressed, and it has been serviceable in such circumstances to be able to point out that a "detention slip" has been issued by the police and that he must wait. But one can manage without this curb.

In one Scottish city all this is the usual practice, when a case of attempted suicide is reported to the police. In another city, when it is, so far as the police know, a case of a first attempt at suicide, the individual is given a "caution" regarding what he has done, but he is not charged. In a third city, the police neither caution nor make a charge, except in the rare

cases where there is a public commotion: they simply bring the individual who has attempted suicide to one of the general hospitals and leave him in medical hands. The attempted suicide is thus treated by the police like anyone else who has suffered an accident or injury and requires medical treatment: they consider him a sick person and take welfare action accordingly. They experience apparently no difficulties due to the individual's non co-operation: and they do not fear being charged with assault. Why should they, what court would listen sympathetically to such an accusation? The police intervene, and so do we all, with the instinct of helping a fellow-man or woman.

There is a small number of people who make repeated and even numerous suicidal attempts, most often temperamentally unstable people of psychopathic or epileptic constitution (Batchelor, 1954). These repeated attempts may constitute a social problem, and certification with admission to a mental hospital is not always possible. In such cases the police may more or less be provoked into bringing and taking to court a charge of breach of the peace; and this may be not unhelpful. The individual may then be placed on probation and may be directed to undergo psychiatric treatment.

In cases of attempted suicide where the individual tries to take his family with him, or other persons are involved, a charge is, of course, made and it goes to court. The survivor of a suicide pact may be charged with manslaughter or with non-capital murder.

In the bringing of a charge of breach of the peace in cases of attempted suicide, we see the relatively innocuous vestiges of a more serious legal attitude to suicide as an offence.[1] The procedure of treating the suicidal individual as a sick person is taking its place; it is already established in large areas of Scotland, and probably it will not be long before this is the common practice throughout Scotland. There is seldom an advantage, and usually definite disadvantages, in charging these people. It comes to the same in the end, the suicidal individual is placed in the hands of doctors in hospital, and it is clear that the public in Scotland, together with the police and the courts, now generally accept this as right and proper.

In 1956, in Scotland there were 397 deaths from suicide in a population of 5,145,000, a death-rate from suicide of 8 per 100,000. In England and Wales the death-rate from suicide at 12 per 100,000 stood 50% higher than that in Scotland. There has been no recent marked alteration in this differential suicide rate, and the number of attempted suicides (which out-number the suicides many times) bears probably a similar relationship to the suicides in both countries. These figures for suicides in the two countries do not on the face of it suggest that Scotland's more permissive legal attitude to suicide encourages these acts. In fact there is no evidence that legal sanctions have a significant effect in inhibiting suicide. Amongst some hundreds of people questioned about their fore-knowledge of the legal implications of their suicidal acts, most replied that the legal aspects of what they were about had not entered their minds. Their acts had been determined by morbid emotions which had gushed up to sweep away judgment and social restraints. Some of those who admitted that they did know that suicide was illegal, said understandably that they had not cared since they had expected to die. There was no evidence that these people had acted as they did because they knew that the legal penalties were negligible. Two-thirds said that they knew that they had acted against the law, a few gave themselves up to the police, but practically no one knew exactly what the law was or how it might affect them. Some thought that they would be put in prison, others that they would be sent to a mental institution. The knowledgeable exceptions were those who had been through it all before.

There is no doubt that many suicidal acts are aimed not purely at self-destruction but are socially orientated, and express either hostility to others or a call for help or both these impulses. Stengel (1952) has made a major contribution to the understanding of their sometimes equivocal nature. Our society should now be mature enough to tolerate the hostility of these acts and to respond constructively to the appeal for assistance, by giving unfettered the medical care and treatment which these sick people need. In Scotland this goal has been more nearly approached than in England.

## REFERENCES

BATCHELOR, I. R. C. (1954) *Brit. J. med. Psychol.*, **27**, 158.
STENGEL, E. (1952) *Proc. R. Soc. Med.*, **45**, 613.

**Dr. Irene M. H. MacAdam, J.P.** (Leeds):

From my early days in general practice and also from the outset as a magistrate I have been impressed by the unfairness of the legal machinery which may operate when a person tries to take his own life. Yet from the limited experience of fifteen years as a Justice of the Peace in Leeds it would appear that the problem of suicide is a small one compared with

other "crimes". As a member of a prison committee concerned with 700 men, one hears of or sees very few attempted suicides—perhaps the occasional case in the prison hospital—while in one particular six months I found only 6 such cases and these were all men on three weeks' remand. I feel that so long as it is possible for a visiting magistrate to find even one case in prison, then an attempt must be made to get this obsolete law changed.

The fact that the numbers throughout the country are not greater is primarily due to the very diverse and inconsistent way in which this law is administered in the cases that are discovered. It is a matter of chance whether such an unfortunate person makes the attempt in a town where the police seldom prosecute or in a place where the police seldom turn a blind eye on anything. A law which is so frequently evaded ought either to be ruled out altogether or at least amended so that it can be properly exercised. It is left to the discretion of an officer in the Chief Constable's department, whether a charge is brought or not.

The reasons usually given for bringing a charge are that it is a second attempt and that the offenders must be protected and treatment secured for them. There are measures well known to the medical profession for coping with the detention of these unfortunates and for their subsequent treatment but not all magistrates appreciate the facilities available. It is hoped that this type of mental illness will be provided for in any new legislation that may arise out of the recent Royal Commission Report on Mental Illness.

When cases are brought up with the idea of securing treatment, a probation order with the necessary "condition" is usually made. Such an order carries with it the sanction that the offender can be brought back to court if he does not fulfil the conditions and accept treatment. The work of probation officers in these difficult cases is of tremendous value but they are handicapped from the outset because the offender has already had to appear in court and perhaps been in prison. I would pay great tribute to the way the probation officers secure the best possible medical and psychiatric treatment for these people but surely it would be more fitting that a psychiatric social worker should be the one to make the enquiries and arrangements for treatment and then do the follow up case-work; at any rate someone who is not a servant of the court should do this work, to help to dissociate the idea from anything criminal. Despite the efficiency of the medical services when the cases become known to them, there may still be a few who escape the medical net or who refuse to be protected against themselves. When the emergency arises then the police must have the legal right to intervene or they would become liable to an action for unlawful arrest or detention. I submit that it would not be difficult for legislation to be evolved so that the police could take action in a manner similar to that used when a young person has to be taken into custody as "being in need of care and protection" or "being in moral danger". It should be possible for adults as well as children to be deemed "in need of care". If some form of legal sanction must be retained then let the person be brought before a Magistrate's court in this way; but personally I deplore the necessity of ever bringing these people into court and inflicting such an ordeal upon them. Should an attempted suicide cause some disturbance of the public peace a prosecution for a breach of the peace could be brought, as in Scotland. This would be tried summarily and would not give the person the stigma of a criminal record for an indictable offence, and so prejudice his future in regard to appointments, emigration, &c.

Many of those who attempt suicide do so for a histrionic purpose; they really have no genuine intention of ending their lives and are therefore not guilty of a "malicious attitude of mind". The onus of proving the charge that the attempt was genuine, is on the prosecution and if this cannot be done, there can be no conviction. In such cases it is particularly unfortunate that they have been charged.

Very few magistrates, or judges in higher courts, ever impose the severest penalties in their powers for this offence but it is surely a poor argument for the retention of these penalties that they need not be used! The court has a wide discretion and can apply any remedy it thinks suitable: absolute discharge, conditional discharge, probation with or without "conditions", or even a fine. Admittedly a properly informed court has ample facilities for very humane and sympathetic treatment.

The argument for retention of the criminal aspect in order to act as a deterrent has been disproved many times. If to attempt suicide is an offence not just against the person concerned but against the society in which he lives, then legally the present law is fulfilling one of its main purposes—to protect society—and it may do this by depriving the individual of his liberty. It is improbable that even the most conservative of legal luminaries will persist much longer in using methods of treatment for society's misfits which are quite contrary to all modern thought. If a moral sense as well as psychological stability is lacking then a court is certainly not the place to start rehabilitation. In the days before the medical profession could provide the knowledge and the means to deal with these cases, the courts had to exercise their power to enforce such treatment as was then available, but the law should now be brought into line with modern thought and attempted suicide should be considered as a medical and social problem and no longer as an indictable offence.

## BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

**Allardt (E.), Markkanen (T.), and Takala (M.).** Drinking and drinkers: three papers in behavioral sciences. pp. 162. Helsinki: Finnish Foundation for Alcohol Studies. 1957.

**Angelov (S.),** and **Kuyumdzhiev (I.).** Leptospirozite u Zhivotnite. pp. 149. Sofia: B'lgareska Akad. Nauk. 1956.

**Asencio-Camacho (F.).** Problemas actuales de sociología médica del Puertorriqueño. pp. 251. Mexico: Gráfica Panamericana. 1957.

**Audy (J. R.),** ed. Malaysian parasites XVI—XXXIV. (Studies from the Institute for Medical Research, Federation of Malaya, no. 28). pp. 471. Kuala Lumpur: Institute for Med. Res. 1957.

**Bopp (C.).** Tratamento da cromoblastomicose pelo calciferol. pp. 183. Porto Alegre: Livraria do Globo. 1957.

**Bray (R. S.).** Studies on the exo-erythrocytic cycle in the genus Plasmodium. (London School of Hygiene and Tropical Medicine, Memoir No. 12). London: Lewis. £2 2s. 0d. 1957.

**British Standards Institution.** Dental amalgam alloy (silver-tin). (B.S. 2938: 1957). pp. 7. London: B.S.I. 3s. 0d. 1957.

**Brod (J.).** Chronische Pyelonephritis. pp. 130. Berlin: Volk u. Gesundheit. 1957.

**Buck (A. E.),** and **Palmer (F. C.).** The clothes of God: a treatise on neo-analytic psychology. pp. 238. London: Peter Owen. 30s. 0d. 1956.

**Centre Internationale de L'Enfance.** Travaux et Documents VII. La carence de soins maternels. pp. 188. Paris: Presses Univ. France. 1955.

**Christensen (P. A.).** South African snake venoms and antivenoms. pp. 129. Johannesburg: South African Institute for Medical Research. 1955.

**Culpepper (N.).** The complete herbal. pp. 603. Wilmslow: printed privately for I.C.I. (Pharm.) Ltd. 1953.

**Deutsche Forschungsgemeinschaft.** Farbstoff-Kommission. Mitteilung 9, 20 Dezember 1956. pp. 28. Wiesbaden: Steiner. 1956.

**Deutsche Forschungsgemeinschaft.** Farbstoff-Kommission. Mitteilung 6. 2nd edit. pp. 151. Wiesbaden: Steiner. 1957.

**Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose.** Tuberkulose-Jahrbuch, 1953-54. pp. 283. Berlin, etc.: Springer. 1956.

**Døssing (J.).** Determination of individual normal weights of school children. pp. 105. Copenhagen: Munksgaard. 15s. 0d. 1952.

**Dureux (E.).** L'electro-encéphalogramme au cours des dégénérescences tapéto-rétiniennes (à propos de 50 observations). Les abiotrophies neuro-rétiniennes. Thèse présentée . . . 1956. pp. 177. Nancy: Univ. de Nancy. 1956.

**Hansen (K. M. M.),** ed. Therapeutische Technik für die ärztliche Praxis. 4th edit. pp. 880. Stuttgart: Thieme. 1956.

**Helwig (B.).** Moderne Arzneimittel. pp. 756. Stuttgart: Wissenschaftliche Verlagsgesellschaft. DM. 68. 1956.

**Jahrbuch der Gesamten Therapie 1956.** pp. 701. Berlin: Duncker & Humblot. 1956.

**Lewis (H. K.) & Co.** Catalogue of Lewis's medical, scientific and technical lending library. New edition revised to Dec. 31, 1956. pp. 1178. London: Lewis. 25s. 0d. 1957.

**Oswald (N. C.),** ed. Recent trends in chronic bronchitis. pp. 199. London: Lloyd-Luke. 30s. 0d. 1958.

**Schmidt (P.-G.).** Die Lungentuberkulose: Diagnose und Therapie. 3rd edit. pp. 384. Stuttgart: Thieme. DM. 58. 1956.

**Sheldon (W. H.).** The varieties of human physique. pp. 347. New York and London: Harper. 22s. 6d. 1940.

**Sheldon (W. H.).** The varieties of temperament. pp. 520. New York and London: Harper. $4.50 (27s. 0d.). 1942.

**Sheldon (W. H.).** Varieties of delinquent youth. pp. 899. New York and London: Harper. $8 (56s. 0d.). 1949.

**Sheldon (W. H.).** Atlas of man. pp. 357. New York and London: Harper. $10 (£4 0s. 0d.). 1954.

# Section of General Practice

President—G. M. KERR, M.B., L.R.C.P., F.F.A.R.C.S.

[*December* 18, 1957]

## DISCUSSION ON THE BREAST IN PREGNANCY AND LACTATION

**Dr. J. C. T. Sanctuary:**

*Notes on the Archæological and Anthropological Approach to the Subject of the Human Breast [Abstract]*

The breasts have held a vital place in the struggle for existence of the human race and it did not escape the observation of primitive man or those of early civilization how essential these organs were to its preservation and propagation.

The maternal breast as a symbol of the goddess of nature played its part among the ancients. Mother Nature herself was moreover regarded as so important that the number of her breasts was increased when portrayed both in drawing and sculpture as in the many-breasted Diana of Ephesus in the Naples Museum.

The reproductive features were further accentuated in portraiture and sculpture by the subject holding her genitals in one hand and a breast in the other. In mediæval and modern times this has been accepted as a covering of modesty but it was not always so, and a number of transitional forms have satisfied the archælogists that so far from being modest this posture was intended to accentuate the features to which the hands pointed.

Breast forms among primitive peoples are very typical of various races and tribes and local variations would also be obvious among members of the higher civilizations if they did not cover the breasts and artificially change their natural shape and position at will.

It is a fact that the more high-bosomed a woman may seem the more her ample bosoms would, if left alone, become dependent members. Primitive races indeed practise a simple form of bust control by tying a string round their pendulous breasts in order that these shall not interfere unduly with their daily activities.

To improve lactation is the object of all peoples by either rational or superstitious means. Studying only the latter we find many and varied substances used to stimulate or inhibit lactation.

There is a general tendency to encourage a grain and fish diet to produce milk while luxury foods are discouraged. Doubtless the fact that the male authorities presumably decide these matters in primitive areas has something to do with this arrangement which must be satisfying to them.

Among many sovereign remedies for poor lactation the following may be mentioned:

(1) Forcing the breasts together and tying them while turning the husband out to starve for seven days (Java).

(2) Stripping naked and waiting for breast irritation to start before suckling the infant (Maori).

(3) Prayers and libations, the suspension of a bag of mercury or an agate (milkstone) round the neck (various areas).

Among the ancients a good deal of sound advice was given. Said the ancient Israelites "When a woman suckles the work of her hands shall be lessened and her food increased."

The custom of keeping the husband aloof from the wife during suckling is widespread. In ancient Peru intercourse was forbidden during the time of lactation for fear of damage to the wife's health and milk production, but the husband was nevertheless encouraged to practise pederasty with his wife at this time. Other rules obeyed during lactation include

feeding the child from one breast only and never using the other (Sicily), forbidding the mother to spin for fear of giving the child vertigo (Transylvania), and feeding the child from the right breast first to avoid left-handedness (Wurtemburg), whilst in parts of Austria two nursing mothers must never drink together or one will drink away the other's milk.

In many places the onset of a menstrual period or a further pregnancy enforces a rule that suckling must immediately be stopped.

As to weaning, occasions recommended vary: the establishment of another pregnancy, a new, rising or full moon, but not a waning one. When the roses are in bloom and on Good Friday under a walnut tree (in Switzerland).

Positions in suckling vary in different areas. These are briefly as follows:

(1) European—The mother holding the child more or less horizontally.

(2) Western Asian and Eastern Europe—The mother hangs over the child which rests undisturbed.

(3) Eastern Asia (Japan)—The mother sits on the ground and the baby is rested on her knees.

(4) Hottentot—The infant is usually carried on the back and the mother throws the very long pendulous breasts which these races develop, over her shoulder and so suckles the child.

The period of time for which suckling continues varies considerably. On the whole, boys are breast fed for longer than girls and the racial extremes vary from Europeans and Hottentots, who suckle their young for less than twelve months, to Eskimos, who will continue up to the age of 15 years.

The treatment and prevention of breast infections have produced a number of interesting ideas. The Styrians poultice the breast with the heated urine of the patient and cool it with iron which has been put on ice. In Serbia the bride does not allow her husband to touch her breasts until after the wedding night. This is done to prevent pain while nursing. In Mecklenburg breasts and face are rubbed with placenta as a prophylactic measure.

There is a widespread and popular idea that it is fatal to the infant to apply a newborn baby to the breast very soon after birth.

Human milk has been used as a magical agency in the treatment of deafness, blepharitis, children's fevers, a badly healing umbilicus after shedding the cord, as an abortifacient, to expel a dead fœtus and as an aid to a normal delivery. Further uses have been in consumption, for the treatment of a rattlesnake bite and for the mutation of human beings to cranes or mushrooms.

In some parts of Africa if a woman suckles herself no husband dare refuse her request, whilst in New Guinea a girl swears by her swelling breasts as a man does by his beard.

The feeding of adults with human milk has been a common treatment of the enfeebled from Greece to Japan. A rather pleasing treatment of the hopeless lover is for him to suckle at his beloved's breast whereupon she becomes his "mother" and the passion is quelled.

Women have suckled animals among savage races in Australia, Polynesia and South America and Asiatic tribes.

In conclusion it is worthy of note that the Greek mythologists decided that Heracles was suckled by Hera as an adult while the sons of Zeus were not allowed to participate in divine worship until they had fed at Hera's breast.

## REFERENCE

PLOSS, H. H., and BARTELS, M. K. A. (1935) Woman, London, 3, 173–244.

**Dr. Mavis Gunther:**

The management of breast feeding is a technical subject in which rather remote theoretical knowledge is of direct practical value and it needs to be learnt by doctors and midwives for, with it, most of the troubles of lactation can be prevented. For instance, an analysis of the part played by instinct in the inception of feeding has clearly defined the objects of antenatal preparation. Both the mother's and the baby's parts can and commonly do fail for want of successful instinctive action and instinct here is found to have much in common with its other manifestations which have been so happily investigated by Lornz, Tinbergen and other workers.

The quality which ethologists observe is behaviour, an activity which is more than a reflex,

usually apparently purposive, appearing for the most part untaught. It is, of course, most easily studied in the newly-hatched or newborn because there is no confusion with other learnt behaviour but very much is also known, even of very elaborate patterns of instinctive behaviour in courtship, mating, nest-making and many other activities. From an immense amount of information, generalizations about instinct have been made which hold true throughout most of the animal kingdom and which are found to have an application in the early activity in the newborn human. Instinctive behaviour is evoked by specific patterns of stimuli, sign stimuli, which work within one sensory system calling out an innate release mechanism. One classical example of this is the attempt at feeding which a newly-hatched gull makes in response to seeing an article resembling an adult gull's bill. Here exact study can be made of the effectiveness of various cardboard substitutes by counting the number of attempts at feeding which a baby bird makes in unit time in response. A picture like a bill is most effective while, surprisingly, the addition of a cardboard representation of the parent bird's head makes no difference. This sign stimulus works entirely within the sense of vision. Other well-known but less exact examples of neonatal behaviour are the newly-hatched duckling's response to spoken duck language, the mechanism being auditory; and the behaviour of the geese described by Lorenz which became permanently attached in their affections to a human if they saw one instead of a goose in their first hours. This last example brings in other characteristics of instinctive behaviour: one is that it is often only evoked at one phase of life and another is that once some instinctive responses have been evoked, the animal's behaviour is altered from that time on.

There are two other characteristics which are relevant to the study of baby feeding: natural sign stimuli can sometimes be outdone by artifacts, by a super-normal stimulus. The well-known example of this phenomenon is the oyster-catcher who, if offered her own nest of eggs or a nest of similar ones made of wood and twice the size, will always sit on the wooden ones. Another phenomenon now recognized in instinctive behaviour is the elaboration of the primary instinctive behaviour by mimicry. Some birds will sing a simple song which is something like a mockery of the species' usual one if the bird is brought up isolated from its kind and the full song is only achieved after listening to others. Similarly some birds will only build token nests if reared without seeing a proper one.

In human behaviour instinct may operate or be lost and for many women the instinctive know-how of feeding has gone. Although a number of cliches can be produced to explain this, more help can be gained by considering a similar situation among chimpanzees. If the female is reared from an early age in captivity she is unable to feed her baby until she has been taught and it is customary now in zoos for a man keeper to stand by ready to teach the newly delivered chimpanzee. As far as I know, those chimpanzees who have known-how of their own accord came to captivity rather later than the others at an age comparable to 7 years in a human. It is likely, then, but there is no scientific proof, that the know-how of the mother's part in feeding which must have been necessary for the survival of each generation depends at least to some extent on mimicry, just as nest building can in a bird. It is quite certain that in chimpanzees, instinct fails the mother and it seems reasonable to expect modern Western mothers who, through present-day standards of modesty grow up without watching feeding from the breast, to have no knowledge of how to feed. It is unkind and decades out of date to count on their knowing.

Most mothers can learn their part rapidly if the baby's feeding behaviour is called into play. If a large number of babies are watched at their first feeds it is seen that many feed quite easily, some cannot and some achieve vigorous feeding only after one identifiable attempt. Successful feeding waits on the occasion when the pattern of tactile and pressure stimuli from the appropriate shape is received within the mouth. If comparison is made between a newborn baby's response to an empty bottle teat and his response to a teaspoonful of milk, the effectiveness of mere shape (the teat) is readily seen whereas a baby does not know what to do with the milk. A survey has been made of the conformity of the mother's breasts immediately after delivery with a device which measured how far the nipple and the tissues behind the areola would pull through a jaw-like gap if gently sucked in. This measured the protractility of the nipple in centimetres and the success or otherwise of feeding was almost entirely predictable from these figures. Where the length was more than a certain figure on this scale feeding was easily achieved, where it was intermediate success could only come if the baby were positioned to get maximum length. Where it was short the baby appeared to feel no urge to feed and stayed apathetically passive at the breast as if it were a premature baby. Where the baby received full oral stimulation, not only did he feed but from then on he would almost put himself on the breast within four or five experiences or sooner.

The physical shape of the breast is thought to be the normal sign stimulus which causes the baby not only to feed but to change in behaviour provided the baby receives it in the

first four days. Without it the baby may remain apathetic and even stay so for weeks. This fact that not only the baby's capacity to get on to the breast but also his eagerness depend on the conformity of the breast is of great practical importance. First, we are thought here to be dealing with realities as inescapable as other natural laws. If a baby does not feed because the breast will not pull far enough into his mouth, nagging will not replace the calling up of eagerness. And when the bottle teat is super-normal to the mother's breast the baby, without any choice, will respond to it and very soon develop a fixed preference comparable to other strong preferences in later life, rather like falling in love.

If, therefore, a mother is to feed her baby, the breasts at the end of pregnancy should offer the nipple as a knob for the baby to centre on and to draw to the back of the mouth, while the areola and the tissues deep to it should be softly yielding and protractile so that nipple and areola together, after passing the 2 cm. gap of the gums, go about 2½–3 cm., into the mouth. This yielding quality should be tested for early in pregnancy and aided by Woolwich shields where there is any doubt. The smaller the nipple the greater the need for compensating pliability in the retro-areolar tissues. The breast can only be assessed by touching, as the outward shape of the breast at rest is little guide. Dr. H. Waller, who invented the shield treatment, estimated that 40% of English primiparæ needed it.

The protractility of the nipple is more effective if the baby is correctly positioned with the lower jaw driving hard at the breast. There should be no gap and certainly no finger between. The ante-natal care and the after-delivery correct positioning bring the added reward that they save the woman from developing the commonest of the four types of sore nipples—the positional sore nipple.

The other main troubles of lactation can also be largely avoided. Engorgement of the breasts in the early puerperium is mostly prevented by giving mothers minute doses of stilbœstrol, 2 tablets of 0·25 mg. being taken an hour or two after delivery and one tablet a day later.

Two kinds of acute mastitis are recognized, the superficial and the intramammary. The superficial is a staphylococcal infection of the skin near or on the areola. It starts as a spot but instead of coming to a head it may track into the breast. It usually comes where staphylococcal infection is already present in the family. It does not cause a rise in temperature and although it can sometimes be aborted by early antibiotics it usually has to discharge before it is cured. It contains pus as soon as it has any body. For prevention a germicidal soap should be used for the washing of the trunk when either the baby or the mother has a staphylococcal lesion. Treatment consists of incision as soon as possible. The course of lactation is only altered by it if the lesion is too close to the nipple or the abscess is allowed to penetrate into the breast.

Intra-mammary mastitis is quite a different disease. It can be characterized by pain, tenderness, a flushed area, a febrile response, a decrease in secretion and there is always a lump. The curious thing about it is that in the early stages if the lump is emptied the condition is usually cured. While the lump is there the patient is liable to have rises of temperature of moderate or considerable severity; rigors are common. The assumption has so often been made that the fever must have a bacterial origin, but this is hard to accept for if the lump is emptied only milk is obtained and emptying brings cure. A careful hunt for organisms by blood culture has failed to find any but if infection comes, the infecting organism is always the staphylococcus. In many years of watching I have never seen a pyæmic abscess result and it seems hard to postulate two organisms, one making the initial febrile stage, the other being a staphylococcus which leaves no trace of the first, or, alternatively, that staphylococci can cause rigors commonly and not cause pyæmia.

A more reasonable explanation of the temperature rise is either that absorption of pyrogenic substances from the pent-up milk can occur—and there are constituents which can reasonably be suspected—or else the distension of the mammary gland causes a neurogenic pyrexia. The patient gives the appearance, as the temperature goes up, of having had an incompatible transfusion. When one remembers the hunt for germs which used to go on when a patient's temperature rose during transfusion before pyrogens or rhesus incompatibility were recognized, legitimate doubts are raised about infection as the immediate diagnosis in the early pyrexia. The raised temperature of early engorgement and of primary acute intra-mammary mastitis are thought to be of a kind.

The clinical finding that if the lump is emptied out immediately resolution is complete but if it is left unemptied for two days it becomes unemptiable now has some experimental backing. Silver has found that in mice if a mammary duct is ligated the capillaries of the blocked alveoli seal off and necrosis sets in. Emptying would then be impossible as the normal process involving blood-borne pitocin could not act.

Intra-mammary mastitis then is pictured as an unemptied part of the gland, increas[illegible]

tension within causing local signs and, by absorption or distension, a febrile response. After two days the chances of cure by emptying become small and staphylococcal infection almost inevitable. Because of the time limit on emptying, treatment is urgent. It consists of an antibiotic cover for, if infection comes, it will be with staphylococci. Emptying of the breasts should be undertaken by putting the baby to the breast, by hands or, most easily, by the Humalactor. Feeding from the breast should usually be continued for two days and then if the condition is not improving lactation must be suppressed. If infection comes lactation should be suppressed as far as possible before incision as otherwise fresh areas of unemptied breast tissue extend the area of mastitis and in turn await infection.

Preventive measures consist of those which ultimately keep the breasts empty. They start with the antenatal preparation, with shields if necessary since they help a baby to feed vigorously. Routine doses of stilbœstrol immediately after delivery help to avoid engorgement. During lactation lumps in the breast should be emptied and mothers should be taught to watch for them. Extra care is needed whenever the secretion is liable to be greater than the baby's demands, where secretion is excessive, the baby indisposed or where supplementary feeds are being given. Above all, breasts must be kept empty while lactation is being suppressed.

REFERENCES


BUDD, A., SMITH, L. G., SHELLEY, F. W. (1943) *Proc. zool. Soc., Lond.*, Ser. A, **131**, 1.

GUNTHER, M. (1953) *Medical World*, **79**, 571.

—— (1955) *Lancet*, i, 574.

—— (1956) *Lancet*, i, 175.

LORENZ, C. Z. (1952) King Solomon's Ring, London. p. 202.

MIDDLEMORE, M. P. (1941) The Nursing Couple. London.

SILVER, I. A. (1956) *J. Physiol.*, **133**, 65 P.

TINBERGEN, N. (1951) Study of Instinct. Oxford.

WALLER, H. (1946) *Arch. Dis. Childh.*, **21**, 1.


**Dr. David Morris:**

The preparatory techniques for breast feeding introduced by Dr. H. Waller at The British Hospital for Mothers and Babies at Woolwich, have made us familiar with some of the factors which impede or aid successful lactation.

Routine ante-natal examination of the breasts ensures the early diagnosis of such anatomical abnormalities as retracted nipples and their treatment with glass or plastic shells. Likewise the detection of inelasticity of the skin forewarns of the possibility of engorgement and its prevention by the early use of stilbœstrol. Manual expression taught ante-natally and practised during the last four to six weeks of pregnancy enables mothers to express without difficulty surplus milk after the baby has fed and thereby avoids rising tension and inhibition of further milk flow. In such conditions as prematurity or birth injury lactation can be established and maintained in spite of the baby's condition.

Breast feeding in present-day society appears to be a task of some difficulty requiring help, guidance and encouraging support in the lying-in period. Many of the failures of breast feeding are due to a lack of adequate supervision and preparatory training. The cracked nipple detected before skin erosion occurs is a common example of an avoidable cause of failure of breast feeding.

The recent survey carried out at Woolwich in conjunction with the sociology department of Bedford College illustrates what can be achieved. In contrast to the national trend of 41% of women fully breast feeding at 8 weeks, 69% of women discharged from hospital fully breast feeding were still doing so at 3 months, and 46% at 6 months.

Little is still known of the cause of failure of lactation in those apparently successfully breast feeding but it may well be that social trends and the ready recourse to bottle feeding is largely responsible. The increasing tendency to introduce early mixed feeding may also be an important factor.

Dr. H. F. Welbourne's study "Bottle Feeding: A Problem of Modern Civilization" amongst the Baganda tribe in Kampala, Uganda, illustrates the influence of the availability of bottles and dried milk. She found an increase from 14% to 30% in five years of supplementary bottle feeds before 6 months with a significant higher incidence of respiratory and bowel disturbances in those bottle fed. The weight gains were 1–2 lb. higher in those fully breast fed.

It is too quickly assumed that women do not wish to breast feed and unless pregnant

mothers are helped ante-natally, and during the lying-in period they may well abandon breast feeding without giving themselves a fair trial. The old reasons for advocating breast feeding, namely the avoidance of respiratory and bowel infections are no longer tenable. But recent work (Sinclair, 1957), and the increasing knowledge of the psychological importance to both mother and child necessitate a closer critical view than is at present held.

## REFERENCES


MORRIS, D., and JEFFEREYS, M. (1958) Breast Feeding, Living Conditions and Health. (In the press.)

Royal College of Obstetricians and Gynæcologists and Population Investigation Committee (1948) Maternity in Great Britain: London.

SINCLAIR, H. M. (1957) *Brit. med. J.*, ii, 1424.

WELBOURNE, H. F. (1958) Bottle Feeding: A Problem of Modern Civilization. (In the press.)


**Dr. Joan Ferreira:**

My point of view has developed while working in maternal and child welfare clinics. For fifty years these clinics have been trying to promote breast feeding, and it is disconcerting to find it steadily declining.

Ross and Herdon (1951) at Bristol found that the incidence of babies breast fed at three months fell from 77% to 36% between 1929 and 1949. During this period the proportion of babies attending welfare centres rose from 27% to 83%.

In recent years attendances at welfare centres over the country as a whole have dropped very slightly, but a large majority of babies do attend. In spite of this it is estimated that less than half, perhaps only a third of babies are breast fed at three months. Reports of various surveys show regional differences and also much greater success in groups having special help, e.g. at Woolwich, and Naish (1949) in her own practice.

The number of babies leaving hospital fully breast fed has also dropped, falling from 86% in 1950 to 76% in 1955. It is interesting to note that only 66% leaving the London undergraduate teaching hospitals were fully breast fed in 1955. I wonder whether this indicates increased readiness to allow mothers to make a choice about the method of feeding, and if so whether more are deciding not to breast feed. The drop may be accounted for partly by a greater tendency to send slightly doubtful cases out on complementary feeds. If so, it is a good sign, as distress in the first week after discharge will be avoided and lactation encouraged.

In all the surveys on lactation at least one-third of mothers were breast feeding; with special help, two-thirds or more were doing so. Nearly one-third are discharged from hospital having failed to breast feed adequately. It looks as though there is a middle third which can be influenced either way by the quality of the preparation and care given.

How might the welfare clinics have done better? I think the teaching given to mothers could have been more effectively and imaginatively done and more widely disseminated. Perhaps the advice given and methods used have at times been at fault. Wickes (1952) criticized these when he pointed out that welfare clinics frequently failed to recognize underfeeding, and in fact tended to induce it by their fear of overfeeding. New ideas are not always acceptable, and it took time for rigid feeding methods to be relaxed. There may have been pressure to continue unsatisfactory breast feeding where efforts to improve the situation had not succeeded. An anxious mother and frustrated baby will harm the attitude of other people towards lactation. Lastly there has been dissipation of effort where the work of the clinic staff has been unrelated to the family doctor.

A woman's emotions are often unstable during the first month after childbirth. She is readily given to tears, feels acutely moved by anything bearing on the baby, is indecisive and finds difficulty in taking responsibility and organizing her household. In order to mother her baby successfully she needs mothering herself. It is important that health visitors and midwives appreciate the kind of care that is needed, particularly in the case of first babies, when the pattern is being set for the rest of the family. Many babies seem to be taken off the breast unnecessarily during this period because of undue anxiety about their progress, misplaced fears about the condition of the mother and want of a little encouragement to persevere. Midwives and health visitors could do much to prevent this.

There should be no break in the care of hospital-confined mothers after they get home and the health visitor should make herself readily available. If possible she should be known to the mother previously, and some hospitals (with the permission of the mother) send information of bookings so that mother and health visitor can get to know each other in good time. Visits should be made at times when they can be most effective and the whole

family should be taken into account, for they are all influencing the outcome of lactation. Midwives and health visitors seem to deal with lactation largely on their own, and I think this may be partly the fault of the medical profession. More interest from the doctor might help to establish more successful nursing couples.

The numbers attending local authority ante-natal clinics have dropped sharply since the National Health Service began, so that clinical care of the breast in pregnancy is a responsibility which is passing elsewhere. If arrangements are reorganized in the future and lead to more continuity of care, this should favour the promotion of lactation.

It has been suggested that the time is coming when patients will cease to attend for clinical examination, and that the clinics will become centres where expectant mothers can learn about the confinement and care of the baby. There is a special need for mothercraft teaching to-day because with smaller families and women working outside the home, girls grow up having little idea of what will be required of them. At present mothercraft classes are held in many clinics by midwives and health visitors but on the whole only a few interested women attend. If all doctors and hospitals caring for primigravidæ appreciated the need for preparation for motherhood, and were satisfied about the quality of the teaching and supervision given, most women would be encouraged to attend.

The planning of the teaching should be personal and understanding. Common difficulties and early discomforts in breast feeding should be discussed and attitudes towards it ventilated. Tact and subtlety have to be used, as it must be recognized that some women will not succeed in lactating. The pleasure and not the duty of suckling ought to be stressed. Although the midwife and health visitor should be the key workers, they should have the support of those members of the medical profession best able to help. There is more to be known about the factors which influence lactation, and mothercraft classes offer a good medium for investigating some of these.

Many factors will have influenced the performance of the breast in lactation before pregnancy starts. As Wickes and Curwen (1957) have shown in comparing breast feeding performance of mothers and daughters, there may be a hereditary factor in ability to lactate. Since bottle feeding has become safer babies of poor lactaters are more likely to survive and pass on this characteristic. The mother's feeding experience in infancy, her growth, nutrition and education and the example of her own mother, will have influenced her abilities and outlook.

Several workers have shown a social class difference in breast-feeding performance, women in the higher classes being more successful. Westropp (1953) felt this emphasizes the need for freedom from domestic worries in the early days of lactation. Hytten and Thomson (1955) suggest that good diet, ability to cope and the belief that breast feeding is best are factors. I have met with an attitude, occurring more commonly in women of Social Classes IV and V, that breast feeding is "not quite nice". Perhaps this is a lingering of the Victorian ideal of refined womanhood which has seeped slowly through society, or possibly it is an awareness of the sensual implications of breast feeding with an unwillingness to admit them. It may be just an acceptable way of expressing failure to breast feed. Many of the women would appear to be complacent about not fulfilling their feminine functions and give up suckling without regret. Some of them believe bottle feeding to be less trouble as the bottle can be propped in the pram. Others do not want to feel "tied" to the baby. Are these attitudes becoming more common and are they being fostered by our present-day society? There is incomplete understanding of women's sexual emotions. Newton (1955) has pointed out the relationship between a woman's attitude to menstruation, sexual intercourse, breast feeding and infant care. Some women feel that suckling their babies is one of the things they expect from life. Mothers who have fed their babies successfully always want to do it again. I am sure that helping a woman to nurse her baby is important to the well-being of both.

There are many ways in which more could be done to encourage lactation. I have only touched on some of those which come within the orbit of the local health services.

## REFERENCES


Hytten, F. E., and Thomson, A. M. (1955) *Brit. med. J.*, ii, 232.

Naish, C. (1949) *Lancet*, i, 146.

Newton, N. (1955) Maternal Emotions. New York.

Ross, A. I., and Herdan, G. (1951) *Lancet*, i, 630.

Vestropp, C. (1953) *Brit. med. J.*, i, 138.

Wickes, I. G. (1952) *Brit. med. J.*, ii, 1178.

——, and Curwen, M. P. (1957) *Brit. med. J.*, ii, 381.

## BOOKS RECEIVED FOR REVIEW

**Abramson (H. A.).** The patient speaks. pp. xxi+239. New York: Vantage Press. $3.50. 1958.

**Andresen (A. F. R.).** Office gastroenterology. pp. xxxiv+707. Philadelphia and London: Saunders. 98s. 0d. 1958.

**Association for Research in Nervous and Mental Disease.** The neurologic and psychiatric aspects of the disorders of aging. Vol. 35. Editors: J. E. Moore *et al.* pp. ix+307. Baltimore: Williams & Wilkins. London: Baillière. 68s. 0d. 1956.

**Beaumont (G. E.).** Medicine. Essentials for practitioners and students. 7th edit. pp. xviii+847. London: Churchill. 45s. 0d. 1958.

**Beckman (H.).** Drugs: their nature, action and use. pp. xvii+728. Philadelphia and London: Saunders. 105s. 0d. 1958.

**Burns (B. D.).** The mammalian cerebral cortex. Monographs of the Physiological Society, No. 5. pp. vii+120. London: Arnold. 21s. 0d. 1958.

**Conn (H. F.),** ed. Current therapy 1958. Latest approved methods of treatment for the practising physician. pp. xxx+827. Philadelphia and London: Saunders. 84s. 0d. 1958.

**Currie (A. R.),** ed. Endocrine aspects of breast cancer. Proceedings of a conference held at the University of Glasgow, 8th–10th July, 1957. pp. xvi+340. Edinburgh and London: Livingstone. 37s. 6d. 1958.

**Davidson (M.).** Memoirs of a golden age. pp. xiii+140. Oxford: Basil Blackwell. 18s. 0d. 1958.

**Diseases of the Colon and Rectum.** Vol. 1, No. 1 January—February 1958. Philadelphia and Montreal: Lippincott. London: Pitman. Annual subscription $12 or £5. 0s. 0d. 1958.

**Edmunds (V.),** and **Scorer (C. G.).** Ideals in medicine. A Christian approach to medical practice. pp. xi+192. London: Tyndale Press. 12s. 6d. 1958.

**Fletcher (P.).** Emotional conflict. pp. vii+158. London: Pan Books. 2s. 6d. 1958.

**Gardiner-Hill (H.),** ed. Modern trends in endocrinology. pp. ix+298+13. London: Butterworth. 65s. 0d. 1958.

**General Medical Council.** British pharmacopœia 1958. pp. xxvi+1012. London: Pharmaceutical Press. 63s. 0d. 1958.

**Gözsy (B.),** and **Kátó (L.).** Studies on phagocytic stimulation. pp. 135. Montreal: Institute of Microbiology and Hygiene of the University of Montreal. 1957.

**Homburger (F.).** The biologic basis of cancer management. pp. xvii+354. London: Cassell. New York: Hoeber. 75s. 0d. 1958.

**Huxley (J.).** Biological aspects of cancer. pp. 156. London: Allen & Unwin. 16s. 0d. 1958.

**Korkis (F. B.).** Recent advances in oto-laryngology. 3rd edit. pp. viii+438. London: Churchill. 60s. 0d. 1958.

**Kruse (H. D.),** ed. Integrating the approaches to mental disease. pp. xvi+393. London, etc.: Cassell. 75s. 0d. 1958.

**Lamb (L. E.).** Fundamentals of electrocardiography and vectorcardiography. pp. xiii+142. Springfield: Thomas. Oxford: Blackwell. 72s. 0d. 1957.

**Levine (S. A.).** Clinical heart disease. 5th edit. pp. vi+673. Philadelphia and London: Saunders. 66s. 0d. 1958.

**Licht (S.),** ed. Therapeutic heat. Vol. II of Physical Medicine Library. pp. xiii+466. New Haven, Conn.: Elizabeth Licht. $12.00. 1958.

**McFarland (B.).** The life and work of Thomas Porter McMurray. pp. 10. Liverpool: Liverpool University Press. 5s. 0d. 1958.

**Raven (R. W.),** ed. Cancer. Vol. I: pp. x+539+19. Vol. II: pp. ix+641+25. London: Butterworth. 85s. 0d. per volume. 1958.

**Rob (C.),** and **Smith (R.),** eds. Operative surgery (in 8 vols.). Vol. 6: Hand, amputation, plastic surgery, gynæcology and obstetrics. London: Butterworth. £5 10s. 0d. 1958.

**Shock (N. W.).** A classified bibliography of gerontology and geratrics. Supplement I 1949–1955. pp. xxviii+525. Stanford, California: Stanford University Press. London: Oxford University Press. 120s. 0d. 1958.

**Smirk (F. H.).** High arterial pressure. pp. xxxvi+764. Oxford: Blackwell. 75s. 0d. 1958.

# Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

[*January* 8, 1958]

## DISCUSSION ON THE COMPLICATIONS OF STEROID THERAPY

**Dr. J. P. Currie** (Glasgow):

The conditions modifying the action of drugs may be summarized thus:

(1) Form, purity and solubility of drug.
(2) Time of administration.
(3) Dose.
(4) Mode of administration.
(5) Rate of uptake.
(6) Efficiency of distribution.
(7) Rate of degradation or inactivation.
(8) Rate of excretion.
(9) Species peculiarities.
(10) Idiosyncrasy.
(11) Cumulation.
(12) Tolerance.
(13) Habituation.

Since these are the factors which may influence the therapeutic efficiency of a drug it follows that they are also the factors concerned in the appearance of the so-called toxic effects.

The matter is, however, more complex than this. It has been demonstrated that substances accepted as being pharmacologically inert are capable of producing "toxic" reactions.

For the purposes of the following examples, "toxic reaction" may be defined as an abnormal subjective or objective phenomenon appearing during the administration of a drug, disappearing promptly on discontinuing the drug and reappearing on subsequent administration.

| No. of patients | Drug | Reaction | |
|---|---|---|---|
| | | Subjective | Objective |
| 100 | Lactose 5 grams | 19 | 4 |

| Nature of reaction | No. of patients |
|---|---|
| Headache | 12 |
| Insomnia | 4 |
| Drowsiness | 2 |
| Itch | 1 |
| Blurred vision | 1 |
| Nausea | 8 |
| Vomiting | 2 |
| Proteinuria | 2 |
| Skin erythema | 2 |

If the medication is administered by injection, however, the incidents of "toxic" reactions increase thus:

| No. of patients | Drug | Reaction | |
|---|---|---|---|
| | | Subjective | Objective |
| 100 | 2 ml. sterile saline I.M. weekly | 34 | 9 |

| Nature of reaction | No. of patients |
|---|---|
| Headache | 16 |
| Insomnia | 6 |
| Drowsiness | 11 |
| Dysuria | 3 |
| Vomiting | 5 |
| Diarrhœa | 1 |
| Proteinuria | 3 |
| Erythema and urticaria | 3 |

Quite obviously, if results of this kind are obtained when using an inert "control" substance, the toxic effects of a known or experimental drug must be measured against such a background and not against an ideal of complete freedom from toxicity.

The appraisal of new drugs is rightly in the hands of practising clinicians, but it is regrettable that so often they appear to lack an adequate knowledge of pharmacodynamics. The modern pattern of our profession's reactions to a new therapeutic substance seems to follow a well-worn path, thus:

(1) Introduction with cautious claims of therapeutic advantage.
(2) Enthusiastic and laudatory papers confirming original claims.
(3) Toxicity reports—ranging from insomnia to sudden death, especially,
  (*a*) blood dyscrasias with special reference to agranulocytosis and aplastic anæmia.
  (*b*) liver dysfunction and jaundice.
(4) Gradual acceptance or abandonment of the drug.

In recent years one has seen this pattern followed with many drugs, among them sulphonamides, thiouracil, chloramphenicol, phenylbutazone, chlorpromazine, and Dichlorophen.

Few drugs produce a specific desirable effect free from side-reactions at any dose level – an example is vitamin C. Fortunately, most have a wide latitude of therapeutic action. That is to say, the effective therapeutic dose is very much lower than the toxic dose for the same drug.

It should be appreciated that toxic reactions recurring during drug therapy may occur in two ways:

(1) As an inherent property of the drug.
(2) As a peculiarity in response by the patient.

The "steroids" used in the treatment of the rheumatic diseases, usually designated the adrenocortical steroids, belong to the group of "$C_{21}$-steroids". They are thus closely related to the other steroid hormones chemically—and this is reflected in their biological relationships also. Thus in adrenalectomized animals the sex hormones have a distinct life-prolonging effect.

It is important to remember that most of the known adrenocortical steroids have the same qualitative effects and differ from one another only quantitatively. The distinction drawn between "mineralo-" and "gluco-" corticoids could only be appropriate when comparing the two extremes of Cortexone and cortisone. The effects of the adrenal steroids may be summarized thus:

(1) Lymphatic involution.
(2) Inhibition of connective tissue proliferation.
(3) Gastro-intestinal effects.
(4) Inhibition of inflammatory, allergic and reactive processes.
(5) Influence on carbohydrate metabolism.
(6) Influence on water and electrolyte metabolism.

Obviously for therapy in the rheumatic diseases we wish to make use of 4 and to a less extent of 1 and 2 above. We particularly wish to avoid effects 5 and 6.

With these requirements in mind two recently introduced synthetic steroids appear most nearly ideal, i.e. prednisone and prednisolone both of which have marked antiphlogistic properties with only minor electrolyte activity.

Unfortunately, some of the most undesirable steroid effects appear to be related to the gluco-corticoid and not the mineralo-corticoid effect, so that the potential of these drugs for producing gastro-intestinal ulceration, delay in wound healing and masking of serious infection remains. Even psychosis, which was at one time thought to be related to interference with potassium distribution appears to be a gluco-corticoid effect.

It has to be remembered that when undesired toxic effects result from the use of a drug the physician and not the drug is most frequently to blame for he should have been aware of the hazards from a knowledge of the pharmacodynamics of the therapeutic weapon he employs.

**Dr. John H. Glyn** (London):

*Incidence—Case Selection—Contra-indications*

A review of the world literature on this subject reveals startling discrepancies in the reported incidence of side-effects occurring during maintenance steroid therapy. Figures ranging from 0–86% have been quoted for *major* side-effects and 33–100% for *all* side effects. These discrepancies have been tabulated and some of the reasons for them discussed

elsewhere (Glyn, 1957). To some extent they can be explained on a purely semantic basis since a side-effect which some would describe as "toxic" would be accepted by others as an *essential—if unwanted—physiological* response to any "glucocorticoid".

Successful maintenance therapy ultimately depends on the balance between the susceptibility of the pathological and non-pathological tissues to the hormones. This balance is *quite impossible to predict in individual* patients but as between different *groups* it is possible with some confidence to anticipate which will incur most problems. Case selection should be based not only on these considerations but also on the prognosis if steroid therapy is not given; hence the importance of recent studies by Duthie *et al.* (1957) on prognostic factors in untreated rheumatoid disease.

Another well-recognized and perplexing fact is that an individual does not necessarily develop the same complication on two successive and apparently identical courses of steroid therapy. Similarly it is not safe to predict the type of complication he will get on the basis of his previous susceptibilities. These points were well made by Lewis and Fleminger (1954) in the psychiatric field but they are equally true in other fields. A possible explanation of these clinical inconsistencies was given by Browne in 1951 when he illustrated that tissue responses to these drugs vary considerably according to the prevailing "milieu interne" of the cells of those tissues.

Now that tuberculosis can be well controlled by appropriate drugs given in association with steroids, there would seem to be no longer any *total contra-indications* to steroid therapy and each case must therefore be assessed according to its *relative* indications and according to the limits of our fallible experience in predicting the expected benefits.

### *Dosage*

Since the incidence and seriousness of side-effects is intimately related to the maximum maintenance dose which is permitted it is important to note that policies on this point vary greatly. Most European centres (e.g. Copeman *et al.*, 1954) state that the incidence of serious complications rises very steeply above a dosage of 75 mg. cortisone/day (or its equivalent of the delta derivatives). Accordingly, they recommend that this should be the maximum permitted dosage. Several centres, working independently of each other, found that the *average* dose in their long-term series worked out at 69·5 mg. cortisone/day. In striking contrast to this, the Mayo Clinic physicians (Polley, 1956) recommend a daily maximum of 30 mg. cortisone for post-menopausal females, 37·5 mg. for younger women and 50 mg. for men. On this regime they claim virtually to have eliminated serious complications but it would seem to some that in many severe cases this can only be achieved at the expense of effective suppression of signs and symptoms.

### *Preparations for Steroid Therapy*

Unless a short course of treatment for a specific purpose is planned, the decision to start a patient on steroids is a major one and should never be taken without full consideration of the implications of long-term and possibly permanent suprarenal suppression. Many clinical, sociological and even economic factors must be evaluated in advance if disappointment and potentially difficult weaning processes are to be avoided. The intelligent co-operation of the patient should be sought and he should have some of the pros and cons explained to him. A careful baseline of objective measurements should be made before treatment commences so that the benefit to him can be accurately evaluated from time to time and the treatment terminated or modified as soon as it seems to be losing its good effect. Above all these drugs must never be used casually or merely as analgesics.

### *Some Specific Complications*

(i) *Steroid "tolerance".*—The concept of the development of tolerance to these drugs is admittedly a controversial one with which to head a list of specific complications. Many would deny that such a condition exists and would argue with conviction that there are many alternative and more satisfactory explanations of the clinical relapses which many patients gradually suffer—despite constant dosage—after the first few months of administration. Hench and Ward (1954) discuss some of these possible mechanisms and Slocumb's (1952) conception of "hypercortisonism" may explain other apparent relapses. Whilst agreeing that there are several possible mechanisms to explain this phenomenon, personal experience suggests strongly that simple drug tolerance can and does frequently develop and indeed that it is probably the most important single cause of the disappointing results of the Empire Rheumatism Council (1955) and Medical Research Council (1957) controlled trials in which cortisone was evaluated against aspirin.

It has been suggested by West (1957) that the relatively better results in the more recent trial in which prednisone was compared to aspirin were due to the greater difficulty experi-

enced by the tissues in adapting themselves to this more "unnatural" steroid. Certainly it is common experience that a patient who has become apparently refractory to cortisone may respond gratifyingly if he is switched to the delta derivatives in corresponding dosage.

In contrast to this, the development of a true resistance to corticotrophin with measurable circulating antibodies is a well-recognized phenomenon. Again the problem may sometimes be overcome by switching to corticotrophin derived from another animal species.

(ii) *Polyarteritis.*—It is now realized that a polyarteritic reaction may be found in biopsy material in about 30% of rheumatoid arthritics irrespective of the treatment they receive. This reaction appears to occur more frequently, in a more necrotizing form, and to be far more widespread in certain patients treated with steroids, especially in those in whom the dosage has been varied too rapidly. Allied to this and of doubtful significance is the acknowledged increase in the proportion of rheumatoid arthritics who show a positive L.E. cell phenomenon when their blood is tested. It is too early yet to be sure of the ultimate fate of these patients, and perhaps one should regard it as an "interesting observation" rather than as a "complication" until this point is settled.

(iii) *Obesity.*—All of the steroid drugs which are used in the treatment of the rheumatic disorders tend to produce abnormal deposits of fat and generalized obesity. Many metabolic factors are concerned in this process. There is also frequently a marked increase in appetite. Since it is so much easier to avoid a patient becoming overweight than to reverse this once it has occurred, it is a wise plan to warn patients of the possibility and to be very strict with them on their initial visits. The problem is slightly less difficult now that the delta derivatives have virtually eliminated sodium retention as a contributory factor.

(iv) *Diabetes* is a relatively infrequent complication (Bishop and Glyn, 1952). There is now universal agreement that it demands a reappraisal rather than the abandonment of steroid therapy in most cases but that every effort should be made to keep the blood sugar under control despite the usual absence of ketosis in this condition.

(v) *Physiological* suprarenal atrophy both during, and for several months after, prolonged steroid therapy is now a well-recognized potential complication unless the appropriate prophylactic measures are taken if the patient meets with any unaccustomed stress. It is strongly recommended that patients carry a card warning any physician or surgeon, who may attend to them casually, that they are receiving these hormones and referring them to an appropriate source of information should they not be aware of these measures.

(vi) *Pregnancy.*—In the dosages now being used, the dangers of producing a malformed fœtus by administering steroids throughout pregnancy if necessary seem to be hypothetical rather than real. Certainly high dosages should not be given except as a life-saving measure. It is interesting in view of the controversy which surrounded this subject in the early days to learn that cortisone has many protagonists as the treatment of choice in cases of toxæmia of pregnancy and it has even been recommended as an aid to conception in cases of relative infertility!

## *Conclusion*

The complications of steroid therapy should be, as Hench once said, "respected rather than feared". As they become recognized and understood, adequate prophylactic measures tend to become available. The secret, as with all complex forms of treatment, is adequate and frequent supervision so that all the side-effects may be tackled in their early stages. This is naturally of particular importance while the patient is being initially stabilized, but throughout the whole of his treatment it is my opinion that no patient should be seen less frequently than once every six weeks, and at each visit he should be routinely and comprehensively surveyed for possible early complications.

## REFERENCES


Bishop, P. M. F., and Glyn, J. H. (1952) *Proc. R. Soc. Med.*, **45**, 168.
Browne, J. S. L. (1951) *Brit. med. J.*, i, 880.
Copeman, W. S. C., Dodds, E. C., Savage, O., Glyn, J. H., and Fearnley, M. E. (1954) *Brit. med. J.*, i, 1109.
Duthie, J. J. R., Brown, P. E., Knox, J. D. E., and Thompson, M. (1957) *Ann. Rheum. Dis.*, 16, 411.
Empire Rheumatism Council (1955) *Ann. Rheum. Dis.*, **14**, 353.
Glyn, J. H. (1957) Cortisone Therapy. London; p. 25.
Hench, P. S., and Ward, L. E. (1954) The Medical Uses of Cortisone. London; Chap. 3, p. 21.
Lewis, A., and Fleminger, J. J. (1954) *Lancet*, i, 383.
Medical Research Council and Nuffield Foundation (1957) *Brit. med. J.*, i, 847.
Polley, H. F. (1956) *Brit. med. J.*, ii, 1253.
Slocumb, C. H. (1952) *Bull. rheum. Dis.*, **3**, 21.
West, H. F. (1957) Communication read to the Heberden Society. Unpublished.

**Dr. F. V. B. Morton** (Nottingham):

With the co-operation of clinicians in various hospitals we have undertaken limited studies on the incidence of and the reasons for peptic ulceration during steroid therapy, in an endeavour to suggest preventive action.

One must, firstly, differentiate between proven peptic ulceration and "dyspepsia" where the presence of actual ulceration has not been shown. This dyspepsia is common during steroid therapy.

Table I gives a rough idea of the figures for the incidence of ulcer in the normal populations of different groups of countries. From Table II it would appear that a slightly higher incidence of peptic ulcer is found in patients suffering from rheumatoid arthritis. This could presumably be due either to aspirin or phenylbutazone therapy or to an inherent tendency for rheumatoid patients to develop ulcer.

TABLE I.—INCIDENCE OF PEPTIC ULCER IN GENERAL POPULATION

| Reference | No. and type of subjects studied | % developing peptic ulcer |
|---|---|---|
| Ivy *et al.*, (1950) .. .. .. | General population of U.S.A., Norway and Denmark .. .. | 1–3 |
| Doll and Avery-Jones (1951) .. | General population of Great Britain aged 15 to 64 .. .. .. | 5·8 male<br>1·9 female |
| Tomenius (1955) .. .. | General population of Stockholm .. | 6·5 male<br>1·9 female |

TABLE II.—INCIDENCE OF PEPTIC ULCER IN RHEUMATOID PATIENTS *not* RECEIVING STEROIDS

| Reference | No. and type of subjects studied | % developing peptic ulcer |
|---|---|---|
| Bauer (1952) .. | Rheumatoid patients *not* receiving steroids .. .. | 4·5 |
| Ragan (1952) .. | Rheumatoid patients *not* receiving steroids .. .. | 8 |
| Kammerer (1957) .. | 33 rheumatoid patients *not* receiving steroids .. .. | 9 |
| Kern *et al.* (1957) .. | 100 rheumatoid patients receiving phenylbutazone .. | 7 |

[A study by Kammerer showed that 31% of 114 rheumatoid arthritics on long-term steroid therapy, 9% of 33 similar patients not receiving steroids and 6% of 33 normal subjects had demonstrable peptic ulcer when all were subjected to barium meal. Incidentally, 3 of the patients receiving steroids were achlorhydric.]

Table III, compiled from the literature, and Table IV, from our own series, show the

TABLE III.—INCIDENCE OF PROVEN PEPTIC ULCER IN PATIENTS RECEIVING STEROIDS

| Reference | Steroid used | No. of subjects and type | % developing peptic ulcer | Duration of therapy (months) |
|---|---|---|---|---|
| Amer. Rheum. Ass. (1955) .. | Cortisone | 546 R.A.* | 6·6% | 12–36 |
| Bunim *et al.* (1955) .. .. | Cortisone | 64 R.A. | 8% | 6–42 |
| Bunim (1957) .. .. .. | Prednisone and prednisolone | 15 R.A. | 27%<br>(4)<br>>20 mg. daily | 12–24 |
| Howell and Ragan (1956) .. | Cortisone or ACTH | 68 R.A. | 26%<br>(18) | 6–42 |
| Sandweiss (1954) .. .. | Cortisone | 500 R.A.<br>480 R.A. | 1·8%<br>5·2% | "Short-term"<br>"Long-term" |
| Kern *et al.* (1957) .. .. | Prednisone or prednisolone | | | 6–59 |
| | >20 mg. daily | 14 R.A. | 21% (3) | |
| | <20 mg. daily | 54 R.A. | 0% (0) | |
| | Cortisone | 72 R.A. | 4% (3) | |
| | Hydrocortisone | 20 R.A. | 5% (1) | |
| Barr (1956) .. .. .. | Prednisone | 16 R.A. | 18% (3) | ? |
| Neustadt (1956) .. .. | Prednisone or prednisolone | 47 R.A. | 4% (2) | >12 |
| Kammerer (1957) .. .. | "Hormone therapy" | 114 R.A. | 31% | ? |
| Henderson (1955) .. .. | Cortisone | 1,440 Various | 5·3% | ? |

*R.A.=Rheumatoid arthritis.

TABLE IV.—INCIDENCE OF PEPTIC ULCERS (INCLUDING HÆMORRHAGE FROM UNKNOWN SOURCE) FOLLOWING TREATMENT WITH CORTICOTROPHIN AND ADRENOCORTICAL HORMONES

| | | | |
|---|---|---|---|
| Corticotrophin | 4 incidents in 299 patients | = 1·3% |
| Cortisone | 22 incidents in 404 patients | = 5·5% |
| Hydrocortisone | 1 incident in 65 patients | = 1·5% |
| Prednisone | 6 incidents in 94 patients | = 6·4% |
| Prednisolone | 8 incidents in 161 patients | = 4·9% |
| Prednisone or prednisolone | 0 incidents in 11 patients | = 0 |

incidence of peptic ulcer in patients receiving different types of steroid therapy. Comparison is difficult because the type and duration of therapy varies, and in the later British series smaller doses and more cautious therapeutic regimes were employed. Bunim's 4 patients who developed ulcer while on delta compounds all received more than 20 mg. daily, as did Kern's 3 patients. None of Kern's 54 patients receiving less than 20 mg. daily developed ulcer. Table III also shows that there is a considerable variation in the ulcer incidence reported by various workers. In one British unit where large doses of prednisolone and cortisone were given to children the incidence of ulcer was 10%. Hydrocortisone appears to give a lower incidence. The impression that corticotrophin results in a lower incidence of ulcer is confirmed by a perusal of the published reports (Savage *et al.*, 1957; West, 1957). The difference between cortisone and prednisolone and prednisone is probably not significant, provided that the difference in potency is remembered. From a study of Table V

TABLE V.—SITE OF ULCERATION

| Treatment | Gastric ulcer | Duodenal ulcer | Both gastric and duodenal ulcers | Gastro-duodenal hæmorrhage | Unknown |
|---|---|---|---|---|---|
| Corticotrophin | 2 | 1 | | 1 | |
| Cortisone | 5 | 9 | | 7 | 1 |
| Hydrocortisone | 1 | | | | |
| Prednisone | 2 | 3 | | 1 | |
| Prednisolone | 4 | 2 | 2 | | |
| Totals | 14 | 15 | 2 | 9 | 1 |

which shows the site of ulceration in relation to the type of steroid used, it is seen that the total incidence of gastric ulcer seems to be approximately the same as duodenal ulcer. As duodenal ulcer is generally more common than gastric it is suggested that the absolute incidence of gastric ulcer is increased. Severe gastric hæmorrhage has been reported in the absence of any detectable localized ulcer, but so also has a type of gastric ulcer which appears to be confined to patients being treated with steroids. These ulcers are of a very acute type, serpiginous and often shallow, with minimal reaction in the surrounding tissues, and often perforate or bleed.

It seems that there may be two types of peptic ulcer which arise as a result of oral steroid therapy: (*a*) The "conventional" duodenal ulcer arising during long-term therapy and possibly associated with alteration in the gastric secretion. Sudden perforation or hæmorrhage may occur as a result of steroid therapy. (*b*) Acute "steroid-induced" gastric ulcers resulting directly from the local action of high concentration of steroid on the gastric mucosa as well as from the systemic action of absorbed drug.

Many conflicting statements have been made with regard to the effect of steroids and adrenal stimulation on the gastric secretion of acid, pepsin and mucin. The evidence available suggests that the increased secretion of acid and pepsin is not necessarily related to the production of ulceration. The decrease in the viscosity of the secretion, reported by some workers, is interesting in view of the suggestion that gastric mucin has a protective action on the mucosa. Such an effect of steroids might be connected with their action on the mucopolysaccharides of synovial joint fluid. It seems more reasonable to suppose that the fundamental alteration in the cell reaction is responsible for the development of peptic ulcer; in other words, that the ulcerogenic tendency of a steroid may be in fact inherent in the therapeutic properties of the drug.

All these factors may be important in the ætiology of steroid-induced ulcers, but it does seem that the reaction of gastric mucosa to high local drug concentrations achieved during oral

therapy may be of the greatest significance. It was thought that enteric-coated tablets or capsules might be a means of avoiding this local factor as the gastric mucosa might be protected in this way from high concentrations of steroid, and it is known that the small intestine is relatively immune to ulceration.

It was necessary in the first place to find out whether satisfactory absorption was obtainable, and in conjunction with Dr. West of Sheffield studies were carried out with two preparations —shellac-coated tablets, and capsules made of formalin-treated gelatin. Figs. 1, 2 and 3

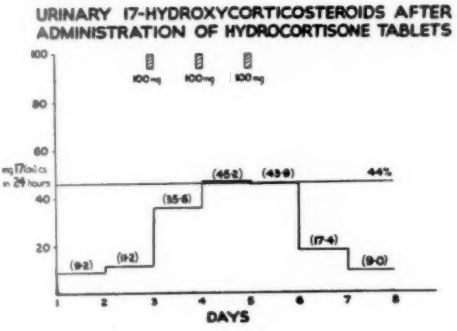



FIG. 1.

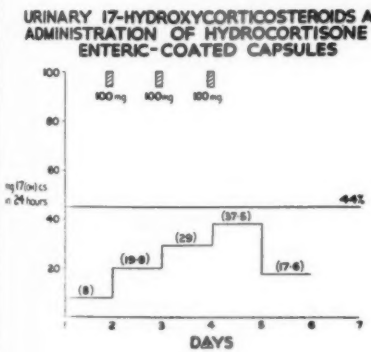



FIG. 2.

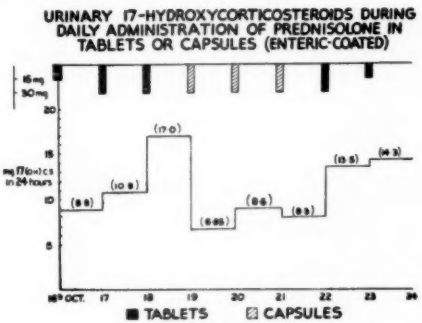



FIG. 3.

show the results obtained by measuring the urinary 17-hydroxycorticosteroid excretion after administration of corticosteroids by mouth. In this laboratory an average recovery of about 44% is expected in a normal individual, and a recovery of less than 44% is considered unsatisfactory. Absorption was found to be variable, but defective in a number of subjects, and patients previously controlled with orthodox prednisolone tablets also had a recurrence of acute joint symptoms when the enteric-coated tablets were administered. These results were disappointing, and it was concluded that absorption of both hydrocortisone and prednisolone from the enteric-coated capsules and tablets used in these experiments was unreliable.

*Summary*

(1) Peptic ulcer with symptoms occurs in a greater number of patients receiving steroid therapy than in a control group. Perforation and hæmorrhage are frequent and severe complications. If proper allowance is made for differing potency, the delta analogues probably give rise to the same number of ulcers as cortisone.

(2) It is suggested the ulcerogenic action of these steroids when given orally is due at least in part to a more powerful local action on the gastric mucosa as well as to the systemic action on cellular function. It is possibly for this reason that injected corticotrophin is less likely to give rise to gastric ulcer than oral steroid administration.

(3) Attempts at modifying the formulation of hydrocortisone and delta-hydrocortisone by means of enteric-coating, in the hopes of ensuring adequate absorption but mitigating the ulcerogenic effect have been unsuccessful.

*Acknowledgment*

I would like to acknowledge with grateful thanks the invaluable assistance given to me by Mr. Raymond Cobb, B.Sc., in the preparation of this paper. I would also like to thank Dr. W. I. Card for his help and for kindly providing material for slides; and Dr. Harry West for allowing me to present results that were obtained in his Unit; and the following for providing data for the analysis of incidence of peptic ulcer during steroid therapy: Drs. Logie Bain, Stuart Barber, Bywaters, Duthie, Dudley Hart, Fletcher, Kellgren, Kersley, Savage and West.

The enteric-coated capsules and tablets used in the studies referred to were provided through the courtesy of Boots Pure Drug Company.

REFERENCES

American Rheumatism Association (1955) *Ann. Rheum. Dis.*, **14,** 325.

Barr, J. H. (1956) *Ann. Rheum. Dis.*, **15,** 397.

Bauer, W. (1952) Proceedings of the Conference on the Effects of Cortisone. Rahway, N.J.: Merck & Co.; p. 56.

Bunim, J. J. (1957) *Bull. N.Y. Acad. Med.*, **33,** 461.

——, Pechet, M. M., and Bollet, A. J. (1955) *Ann. Rheum. Dis.*, **14,** 102.

Doll, R., and Avery-Jones, F. (1951) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 276.

Henderson, E. (1955) *J. med. Soc. N.J.*, **52,** 609.

Howell, D. S., and Ragan, C. (1956) *Medicine, Baltimore*, **35,** 83.

Ivy, A. C., Grossman, M. I., and Bachrach, W. H. (1950) Peptic Ulcer. London.

Kammerer, W. (1957) 9th Int. Cong. Rheum. Dis. Toronto.

Kern, F., Clark, G. M., and Lukens, J. G. (1957) *Gastroenterology*, **33,** 25.

Neustadt, D. H. (1956) *Ann. Rheum. Dis.*, **15,** 397.

Ragan, C. (1952) Proceedings of the Conference on the Effects of Cortisone. Rahway, N.J.: Merck & Co.; p. 55.

Sandweiss, D. J. (1954) *Gastroenterology*, **27,** 604.

Savage, O., Chapman, L., Robertson, J. D., Davis, P., Popert, A. J., and Copeman, W. S. C. (1957) *Brit. med. J.*, ii, 1257.

Tomenius, J. (1955) *Acta med. scand.*, **152,** 391.

West, H. F. (1957) *Ann. Rheum. Dis.*, **16,** 322.

# Section of Dermatology

President—JOHN T. INGRAM, M.D., F.R.C.P.

[*October* 17, 1957, continued from March *Proceedings*, p. 175]

Dr. J. T. INGRAM delivered a Presidential Address on **Famous Dermatologists of the Past.**

[*November* 21, 1957, continued from March *Proceedings*, p. 176]

**Scleredema [Buschke].**—C. M. VESEY, M.R.C.S., L.R.C.P. (for C. D. CALNAN, M.R.C.P.).

V. A., female, aged 29.

*History.*—July 1957: Sudden onset of stiffness of the neck. The stiffness and hardening of the skin spread rapidly over the front of the chest and down to the scapulæ.

She had a mild sore throat about a week previously.

*On examination.*—There is a hardness and swelling of the skin over the neck and front of the chest from the jaw-line down to the 3rd rib, and to a similar level at the back. There is little visible change except for a shiny appearance, and pitting œdema is absent.

No abnormality was found on general examination.

*Investigations.*—X-rays of chest and cervical spine, blood count, and sedimentation rate are normal. Creatine excretion is not increased. Anti-streptolysin titre 120 units/c.c. W.R. and Kahn negative. Rose's euglobulin test negative. Serum proteins normal except for slight increase in gamma globulin.

**Œdematous Scleroderma.**—C. D. CALNAN, M.R.C.P.

T. L., male, aged 52.

*History.*—Five months ago he began to complain of irritation and a rash on the front of his legs. He may have had hardening of the skin previously but the more recent blistering and œdema made him seek advice. About a month ago he had an attack of influenza and urticaria which has now subsided. He next developed a virus pneumonia. Since then his legs have become worse and he now complains of swelling and stiffness of his hands and stiffness of the upper arms and backs of the thighs.

*On examination.*—The lower legs are almost entirely covered by sclerodermatous skin, with pitting œdema and some hæmorrhagic bullæ. The œdema is in many places very superficial, like that found in lichen sclerosus et atrophicus. There are patches of hard skin without epidermal change on the thighs and arms and wrists. Œdema is present over the dorsa of both hands and the clenching of his fists is limited.

*Comment.*—This case contrasts well with the previous one of scleredema (Buschke) because some authors described the latter condition as œdematous scleroderma. This present case has in fact very œdematous scleroderma with gross pitting, œdema, bullæ and hæmorrhages. It is similar to a patient that I showed with Dr. M. Feiwel a few years ago.

REFERENCE

FEIWEL, M., and CALNAN, C. D. (1956) *Proc. R. Soc. Med.*, **49**, 236.

The following cases were also shown:

**Peculiar Widespread Hæmangioma.**—Dr. J. R. SIMPSON.

**Callosities. ? Yaws.**—Dr. J. S. PEGUM.

**Plantar Hyperkeratosis. History of Yaws.**—Dr. R. D. CATTERALL (introduced by Dr. J. S. PEGUM).

**Eruptive Collagenosis.**—Dr. C. D. CALNAN and Dr. H. HABER.

(1) **Deodorant Granuloma of the Axillæ.** (2) **Contact Dermatitis from Neomycin.**—Dr. C. D. CALNAN and Dr. I. SARKANY.

**Ulerythema Ophryogenes.**—Dr. J. H. ALLISON (for Dr. F. RAY BETTLEY).

**Ulerythema Ophryogenes.**—Dr. R. H. MEARA.

**Leishmaniasis.**—Dr. C. D. CALNAN.

**Atrophie Blanche.**—Dr. P. HALL-SMITH.

**Non-suppurative Panniculitis.**—Dr. R. G. HOWELL (for Dr. R. T. BRAIN).

[*December* 19, 1957]

**Alopecia Mucinosa (Pinkus).**—I. MARTIN-SCOTT, M.D.

MRS. S. H., aged 35. Housewife.

*History.*—Early in March 1957 this woman developed two circinate scaly lesions on the nape of the neck which were slightly irritant. She lives on a farm. In August she noticed her eyebrows became slowly swollen, and about one month later the hairs were shed. Gradually this tissue swelling appeared on her cheeks and chin. Her general health throughout had been good.

*Past health.*—Uncomplicated chicken-pox, whooping-cough and measles in childhood. Two children aged 7½ and 1½ years.

*On examination* (2.9.57).—There were two circinate scaly patches in the nuchal area which resembled tinea circinata. There was no fluorescence under Wood's light, and examination of scrapings by Dr. Jacqueline Walker was negative for pathogenic fungi. These lesions were treated with Tineafax ointment and improved, but left in their wake a confluent area of keratosis pilaris devoid of hair. At this time she also had discrete symmetrical indurated swelling of the eyebrows and chin with hair loss, erythema and superficial fine scaling. The follicular ostia were patulous.

When seen on 1.10.57 these firm swollen areas had become more diffuse and extended down her cheeks to the sides of the neck; and by the end of the month, when the biopsy was done, symmetrical small infiltrations were present on both elbow folds. In December 1957 the skin infiltration became less prominent, but involved most of the facial skin excluding the eyelids and nose, but she had developed irritation of both arms, which was considered exogenous and quite unassociated with the main skin condition.



FIG. 1.—December 1957: This shows thickening and scaling of the skin. The eyebrows are lost, and the scalp hair is receding. The biopsy scar is seen on the left cheek.

*Investigations.*—Scrapings from the neck (2.9.57): No pathogenic fungi found. E.S.R. (4.9.57) 14 mm. in one hour (Wintrobe). Mantoux reaction 1/1,000 (4.9.57) negative. Tonsillar swab (4.9.57): *Streptococcus viridans* cultured. Blood count (4.9.57): No anaemia and normal white cell count. X-ray of chest (26.8.57): No abnormality detected. Biopsy from skin of cheek, 29.10.57 (Dr. Charles Pike, Watford): The essential process is a proliferation of the cells of the external root sheaths and sebaceous ducts. Between these cells are multifocal accumulations of a mucinous fluid, with formation of small cysts in places. This mucinous substance is metachromatic with thionine and stains with alcian green. It is, however, only weakly positive by PAS and muci-carmine staining. It gives therefore the reaction of a connective tissue mucin. In the corium around the affected hair follicles and blood vessels there is a light infiltration by lymphocytes with an occasional eosinophil and histiocyte. The epidermis shows a few foci of parakeratosis only.

*Treatment.*—During September 1957 she took 150 mg. chloroquine twice daily, and applied Tineafax ointment to the nuchal area. No treatment has been given since October 195

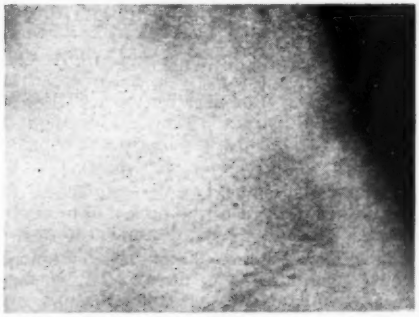


FIG. 2.—This shows the keratosis pilaris appearance in the nuchal area.



FIG. 3.—Low-power view (×15) showing follicular proliferation and loss of hair shafts. Cystic spaces are present in the pilo-sebaceous complex.

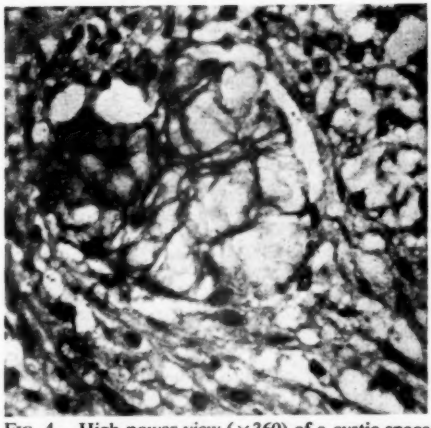


FIG. 4.—High-power view (×360) of a cystic space in the follicular sheath containing mucin.

Figs. 3 and 4 are stained with phloxine tartraxine and alcian green.

*Comment.*—This case is similar to six other cases recently published (Pinkus, 1957). Clinically at different stages of the disease process the features are surprisingly variable, and my case has presented the morphology of tinea circinata, keratosis pilaris, and in the early stages lupus erythematosus profundus with associated alopecia. Histologically the first stage appears to be a true cellular proliferation of some of the hair follicles associated with loss of hair. Next a mucin-containing fluid separates these cells and forms pools within the pilo-sebaceous apparatus, and the sebaceous glands disappear. The infiltration appears to be a reactive phenomenon, and in the cases reported varies from a few lymphocytes to a granuloma. The staining reactions of the mucin in this case are those of connective tissue mucin, which suggests a degenerative pathological process rather than an active metaplasia in which the epithelial cells actually secrete mucin.

POSTSCRIPT (February 1958).—The eczematous condition of the arms settled down in a week, and was probably due to a woollen cardigan. The skin of the face is now less thickened and more mobile, but there has been no regrowth of hair and the keratosis pilaris of the neck remains unchanged. There has been no extension of the disease for three months.

## REFERENCE

PINKUS, H. (1957) *Arch. Derm. Syph. Chicago*, **76**, 419.

**Dr. Brian Russell:** Dr. P. M. Deville recently asked me to see a patient with erythematous plaques on her cheeks. Biopsy showed the same mucinous degenerative changes in the sebaceous glands. I think a better term would be follicular mucinosis, because alopecia is not always seen.

**Normocholesterolæmic Xanthomatosis.**—P. F. BORRIE, M.D.

Miss M. M., aged 49. Stenographer.

*History.*—Two patches of yellow discoloration appeared at the corners of the eyes in 19[illegible]. Since then others have appeared on the face, scalp, neck and chest, some of which have slowly spread. The lesions have been stationary for the last three years. For the last four years she has been getting periods of pyrexia. They last for about five weeks at a time, are accompanied by little malaise, but the temperature may be as high as 101° F. at night.

*Past history and family history.*—Not relevant.

*On examination.*—There is a barely palpable, soft, well-defined yellow infiltration of the skin, confluent over the whole scalp, front of the neck and upper part of the centre of the chest, and patchy on the face. General physical examination showed no abnormality.

*Investigations.*—Serum cholesterol 250 mg./100 ml. Hæmoglobin 76%. R.B.C. 3,800,000. W.B.C. 4,000 (neutros. 49%, lymphos. 45%, monos. 5%, eosinos. 1%). E.S.R. varies between 40 and 70 mm. in the hour (Westergren). Plasma proteins (electrophoresis): Slight increase in gamma globulin.

Blood sugar (fasting): 122 mg./100 ml.

Liver function tests normal.

X-ray chest: Local bulge of ascending aorta, probably arteriosclerotic. Lungs, bones: Normal.

*Biopsy:* Xanthomatous deposit in the corium, most of the lipoid material being present in large foamy macrophages, amongst which there are numerous Touton giant-cells. Frozen section shows the sudanophil material to be doubly refractile: i.e. cholesterol.

*Comment.*—Cutaneous deposits of cholesterol associated with normal levels of cholesterol in the blood usually occur as small lesions on the eyelids (xanthelasma) or as xanthoma disseminata. In the latter form the nodules may be isolated, pedunculated or packed together. They occur mostly in the axillæ, antecubital fossæ or on the sides of the neck. Even where the individual lesions are packed so closely together as to appear confluent, stretching the skin always shows up the furrows between them. I have been able to find only two examples in the literature with a similar type of cutaneous lesion to the present case (Thannhauser, 1950). One was a man of 55 in whom the lesion covered nearly the whole body. He died two years later of multiple myeloma, but showed at post-mortem examination no other xanthomatous deposits. In the second case the xanthoma covered the whole of the scalp, but was associated with multiple petechiæ on the trunk and limbs, dural, cerebral and lymph-gland xanthomatosis and eosinophilic granulomata of bone. Although no evidence of other xanthomatous or granulomatous deposits has been found in the present case, the history of recurrent pyrexia and the consistently high E.S.R. suggest that these may, in fact, be present.

REFERENCE

THANNHAUSER, S. J. (1950) Lipoidoses. 2nd edit. New York.

**Livido Reticularis.**—P. F. BORRIE, M.D.

Mrs. M. N., aged 37, housewife.

*History.*—1948 (one year after birth of last child): Red, tender, indurated nodules in right leg, diagnosed as phlebitis. 1951: Same condition in left leg. 1953: Development of livido reticularis, reaching its present extent in a year.

July 1955: Onset of ulceration while in Germany. Since then has had 3 further crops in Singapore in June, September and October 1956, and 2 in England in July and October 1957. The ulceration lasts one to two months. It begins with purpura and telangiectasis, proceeds to hæmorrhagic blister-formation and exquisitely painful superficial ulceration. The pain, which in the last attack needed heroin to control it, is worse with the leg up and with warmth.

*Past history and family history.*—Not relevant.

*Treatment.*—Vasodilators, lumbar sympathectomy, steroids, mepacrine with no effect. Two weeks ago fresh signs of impending ulceration occurred, which disappeared in a week with heparin 10,000 units six-hourly.

*Investigations.*—Full blood count, E.S.R., W.R., Kahn, plasma proteins, cryoglobulin and cold agglutinins, normal. L.E. cells—none. Muscle biopsy, and urinary 5-hydroxyindole and acetic acid: normal. Biopsy from base of ulcer: fairly marked obliterative endarteritis but this is compatible with changes secondary to the chronic ulceration.

*On examination.*—Livido reticularis from feet to waist and from hands to shoulders. Pigmented and depigmented, atrophic scars on feet and lower legs in sites of previous ulceration, some of the "atrophie blanche" type.

*Comment.*—This appears to be a good example of the primary vascular, as opposed to the symptomatic, variety of livido reticularis. A small proportion of these cases are worse in the summer and 12 almost identical cases were recently described by Feldaker *et al.* (1955). The treatment of choice was found to be bed rest, elastic bandages and hexamethonium. Sympathectomy was disappointing, but heparin was not tried.

REFERENCE

FELDAKER, M., HINES, E. A., and KIERLAND, R. R. (1955) *Arch Derm. Syph., Chicago*, **72**, 31.

**Gougerot's Maladie Trisymptomatique with Cryoglobulinæmia.**—D. C. G. BETT, M.R.C.P. (for STEPHEN GOLD, M.D.).

Miss P. C., aged 44.

*History.*—For three years she has had recurrent purpuric and urticarial-type lesions on her legs, accompanied by swelling of the ankles. In the last year a small ulcer developed on the lateral side of the right ankle, but this is now healing. Biopsy (October 1954) showed an acute arteriolitis compatible with maladie trisymptomatique (Dr. H. Haber).

*Previous history.*—In 1938 she had an infected parotid gland, and since then has had a dry mouth and also some dryness of the eyes, with occasional pain and swelling of the parotids. Since 1953 she has had attacks of stiffness, pain and swelling in the joints of her hands and in the knees and ankles, but this clears completely between attacks. She has been diagnosed as a case of Sjögren's syndrome. In 1953 she had sinusitis, but has had no recurrences. Since 1944 she has had carious teeth, but these were removed in 1955.

*On examination.*—No abnormality detected apart from the leg lesions.

*Investigations.*—Hæmoglobin 86%; W.B.C. 6,000, with normal differential count. Bleeding time: 2 minutes 30 seconds. Clotting time: 10 minutes 30 seconds. E.S.R. 32 mm. in the first hour (Westergren). No L.E. cells. Urine: No albumin, Bence-Jones proteose or sugar. Centrifuged deposit of epithelial cells and occasional polymorphs.

X-rays of chest normal. Bones and skull normal except for some general osteoporosis; no evidence of arthritis or myelomatosis.

Serum protein: Total 6·5; albumin 3·8, globulin 2·7, (alpha-one globulin 0·2, alpha-two globulin 0·5, beta globulin 0·6, gamma globulin 1·4) g./100 ml., cryoglobulins present.

*Comment.*—The cryoglobulin is present in very small amount, much less than occurs in multiple myelomatosis or essential cryoglobulinæmia. It precipitates fully after forty-eight hours at 4° C. and is thus unlikely to cause symptoms in cold weather. In this case the associated Sjögren's syndrome may be regarded as the cause of the cryoglobulinæmia, but another five cases of maladie trisymptomatique, seen at St. John's Hospital for Diseases of the Skin, have had serum proteins estimated and one of these also shows cryoglobulin. This latter case has been extensively investigated without finding any cause for the cryoglobulinæmia except the maladie trisymptomatique.

**Cryoglobulinæmia and Reticulosis.**—E. N. M. JOHNSTON, M.R.C.P., and H. J. WALLACE, M.D., F.R.C.P.

Mrs. M. S., aged 47.

*History.*—Since 1940 attacks of urticaria, described by the patient as itching hives, have recurred in cold weather. Since 1947 recurrent painful ulcers have been present on the legs. Painful discoloured patches appear and break down, leaving ulcers which are slow to heal. During the past six years Raynaud attacks precipitated by cold have affected the fingers. In 1951 bilateral lumbar sympathectomy was performed with apparently little influence on the occurrence of the leg ulceration. In 1952 left cervical sympathectomy produced only temporary relief of the Raynaud attacks. In 1953 an abnormal serum globulin was found but electrophoresis did not confirm the presence of cryoglobulin. Since 1954 courses of isoniazid and PAS have been given, a diagnosis of papulonecrotic tuberculide having been made. At times these drugs have appeared to accelerate healing. January 1957: X-ray of painful left foot showed arthritis of the subtaloid joint. A tuberculous aetiology was suggested. Subsequent X-rays have shown no abnormality. A course of streptomycin in August 1957 was followed by a toxic erythema and all antituberculous treatment was stopped and a course of deltacortisone was given. There have been no gastro-intestinal, cardiorespiratory, neurological or genito-urinary symptoms. There have been joint pains apart from pain in the left foot.

***Past history.***—1951: Pneumonia.

***Family history.***—The patient's three children and sister, all apparently normal, have been investigated for cryoglobulins. None was found.

***On examination.***—The lower legs showed healing ulcers, scarring, patchy discoloration, purpura and pigmentation. A moderate degree of cutis marmorata was present up the front of her legs. Peripheral pulses were present and there were no varicose veins. The hands showed sluggish circulation and shiny atrophic skin of the finger tips. The spleen was just palpable on inspiration. Small glands were present in the neck and axillæ. There were no other abnormal physical signs. The blood pressure was 105/65. No albuminuria or glycosuria was present.

*Investigations*

*Hæmatology.*—Hb 95%. W.B.C. 7,500, normal differential. E.S.R. 50 mm. in one hour (Westergren), 2 mm. in half hour, 22 mm. in one hour (Wintrobe); Platelets 170,000/c.mm. Osmotic fragility of red cells normal. Direct Race-Coombs test negative. No L.E. cells found on three occasions in peripheral blood. No cold agglutinins detected. Bone-marrow: "Marked increase in eosinophilic granulopoiesis but otherwise normal. No plasma cells seen. Very occasional intracytoplasmic deposits of blue homogeneous material are seen in the polymorphs and they may possibly represent deposits of phagocytosed cryoglobulin."

*Serology.*—W.R., P.P.R. negative.

*Biochemistry.*—Plasma proteins: Thymol turbidity 14 units, total protein 6·4, albumin 4·1, globulin 2·3 g./100 ml. Serum electrophoresis: low gamma with an increased alpha 1, beta, and intermediate band between beta and gamma globulins suggestive of the presence of cryoglobulin. This was confirmed by dissolving the cold precipitated protein and re-examining electrophoretically. Cryocrit estimation 14 units. Cryoglobulin estimated accurately (by micro Kjeldahl method) 0·5 gram%. Alkaline phosphatase 6·0 K.A. units, acid phosphatase 1·0 K.A. unit. No protein in urine.

*Radiology.*—Chest X-ray: no lung lesion. Left ankle: no definite bony abnormality. Barium swallow: no evidence to suggest scleroderma of œsophagus. Dilatation of the gullet just above the diaphragm thought to be a phrenic ampulla and no evidence of a hiatus hernia. No reflux could be elicited. Skull, spine, pelvis—no evidence of multiple myeloma deposits.

*Histology.*—An enlarged lymphatic gland was removed from the right axilla and was reported by Dr. I. W. Whimster as showing histological changes suggestive of a reticulum-cell sarcoma or typical Hodgkin's disease.

The following cases were also shown:

**Addison's Disease.**—Dr. R. M. B. MacKenna.

(1) **Prurigo Lymphatica.** (2) **Multiple Kerato-acanthomata.**—Dr. P. F. Borrie.

**Steatocystoma Multiplex.**—Dr. E. Lipman Cohen.

**Chronic Lymphatic Leukæmia with Sarcoidosis.**—Dr. A. Scott.

**Lupus Erythematosus.**—Dr. P. Hall-Smith.

**Chancriform Pyoderma.**—Dr. W. Frain-Bell.

**Idiopathic Trichoclasia.**—Dr. Brian F. Russell.

**Case for Diagnosis. ? Sporotrichosis.**—Dr. M. Feiwel and Dr. R. G. Howell.

Dr. C. A. Clarke read a short paper entitled **Neoplasms of the Gastro-intestinal Tract Associated with Inherited Abnormalities of the Skin.**

# Section of Urology

President—LESLIE N. PYRAH, M.Sc., Ch.M., F.R.C.S.

[*January* 23, 1958]

## Urinary Colloids [*Abstract*]

By N. F. MACLAGAN, M.D., D.Sc., F.R.C.P.

*Department of Chemical Pathology, Westminster Medical School, London*

THE colloidal properties of urine have attracted attention for many years and have formed the basis of two apparently contradictory theories of the pathogenesis of renal calculi. Thus Joly (1931, 1939) and Butt *et al.* (1952) consider that urinary colloids have a protective action by delaying the precipitation of insoluble substances. On the other hand Boyce *et al.* (1954) described in the urine of their calculous patients a gross excess of mucoprotein, which was assumed to act by forming an insoluble calcium complex.

Studies on urinary mucoprotein secretion previously reported from this department (Lockey *et al.*, 1956) indicated a slightly lowered excretion in certain cases of renal calculi and appeared to favour the first of these theories, but no general method for assessing the "protective colloid efficiency" (P.C.E.) of urine was available at that time. Such a method was accordingly devised in collaboration with Dr. A. J. Anderson and is published in detail elsewhere (Maclagan and Anderson, 1958*a*). In brief this method consists of adding solutions of calcium chloride and sodium phosphate to a buffered preparation of dialysed urine, followed by centrifugation under controlled conditions. The amount of phosphate remaining in the supernatant fluid is then estimated by a standard method and gives a measure of the protective colloid efficiency. Values for P.C.E., expressed as $\mu$g.P/100 ml. of dialysed urine, are normally from 0 to + 400 (240 $\pm$ 39) but may vary pathologically from — 200 to + 2,000.

In assessing the results it was found to be essential to separate cases with proteinuria from those without, as the presence of albumins and globulins was usually associated with abnormally high P.C.E. values. In 13 cases of renal calculi without proteinuria the results were slightly below normal (144 $\pm$ 46 $\mu$g.P/100 ml.) but the difference was not statistically significant, and only two of these cases gave results actually below normal limits. Most of the other pathological states studied gave a proportion of high values for P.C.E., a tendency which was particularly marked in rheumatism and cancer. A few abnormally low values were, however, also recorded, e.g. in peptic ulcer and in paraplegia. It was particularly noteworthy that no high values either for P.C.E. or for any of the colloidal constituents were recorded in cases of renal calculi without proteinuria.

Parallel with the P.C.E. tests, estimations of various colloidal constituents were made and the P.C.E. was found to be positively correlated with most of these such as nitrogen, reducing activity, sulphur, hexosamine, and sialic acid.

The results as a whole suggest that many different urinary colloids have some protective action in diminishing the precipitation of sparingly soluble substances, but no significant alteration in this property was demonstrated in cases of renal calculi. Equally, no increase of any colloidal substance seemed to be present, so that in this series at least there is nothing to support either of the two theories referred to above. It appears to be most important for any future studies of urinary colloids to take account of the dominating influence of clinical proteinuria, which, when present, is usually associated with an increased excretion of many proteins and mucopolysaccharides which must obscure the original picture.

A fuller account of these results will appear elsewhere (Maclagan and Anderson, 1958*b*). I am much indebted to the staff of the Westminster Hospital Group and also to Drs. A. R. Harrison and Barbara Billing for the collection of urine samples. The work was supported by generous grants from the British Empire Cancer Campaign and from the Endowment Funds of Westminster Hospital.

### REFERENCES

BOYCE, W. H., GARVEY, F. K., and NORFLEET, C. M. (1954) *Exp. Med. Surg.*, **12**, 450.
BUTT, A. J., HAUSER, E. A., and SEIFTER, J. (1952) *J. Amer. med. Ass.*, **150**, 1096.
JOLY, J. S. (1931) Stone and Calculous Disease of the Urinary Organs. St. Louis; p. 30.
—— (1939) 7th *Congr. Soc. int. Urol.*, p. 77.
LOCKEY, E., ANDERSON, A. J., and MACLAGAN, N. F. (1956) *Brit. J. Cancer*, **10**, 209.
MACLAGAN, N. F., and ANDERSON, A. J. (1958*a*) Ciba Foundation Symposium on The Chemistry and Biology of Mucopolysaccharides. London; p. 268.
——, —— (1958*b*) *Brit. J. Urol.* (In press.)

# Bilateral Orchidopexy and Fertility

By J. H. CARVER, T.D., F.R.C.S.

*London*

FEW papers have been published on the fertility of men who have had bilateral orchidopexy. This is not surprising as the operation even in children's hospitals is not a very common procedure and owing to the long interval between operation and the individual's marriage, contact between him and the surgeon is usually lost. The establishment of sterility clinics affords an opportunity to study the problem. At Hammersmith Hospital over 2,000 men have been seen at the Sterility Clinic between June 1946 and June 1957. 13 of these patients had bilateral orchidopexy. The operations were done at various hospitals in the United Kingdom and abroad (none was performed at Hammersmith) and details of the technique employed were unavailable in most cases. The position and size of the testes when seen at the Clinic and the results of semen analyses are shown in Table I. Of these patients only one operated on at 5 years of age at a Children's hospital was fertile. In this case the left testis was normal whereas the right was in the canal.

TABLE I.—SEMEN ANALYSES IN 13 ADULTS AFTER BILATERAL ORCHIDOPEXY

| Case No. | Age at operation | Gross appearance of testicles at fertility clinic | Semen analyses |
|---|---|---|---|
| I | 5 | Right in canal | 82 million per ml. |
| | | Left + | |
| II | 13 R | Right ¾ | 750,000 per ml. |
| | 14 L | Left ¾ | |
| III | 5 | Right + | Azoospermia |
| | | Left + | |
| IV | 10 | Right ¾ | ,, |
| | | Left ¾ | |
| V | 15 | Right ¾ | ,, |
| | | Left ½ | |
| VI | 12 R | Right + | ,, |
| | 15 L | Left ½ | |
| VII | 15 | Right ¾ | ,, |
| | | Left in canal | |
| VIII | 16 | Right ½ | ,, |
| | | Left ½ | |
| | | Both at external ring | |
| IX | 10 R | Right + | ,, |
| | 18 L | Left ¾ | |
| X | 12 | Right ¾ | ,, |
| | | Left ¾ | |
| XI | 15 | Right + | ,, |
| | | Left + | |
| XII | 17 | Right ¾ | ,, |
| | | Left ¾ | |
| XIII | 8 R | Right ¾ | ,, |
| | 13 L | Left ¾ | |

The second patient had severe oligospermia, 750,000 sperms per ml. He had a course of hormone treatment at the age of 6. Operation was performed on the right side at 13 and on the left at 14. Both testes were about three-quarters of the normal size.

Of the remaining 11 patients 1 was operated on at 5 and the others between 8 and 18. In Case VIII both testes were atrophied and were just at the external ring. In Case VII the right was in the scrotum and the other in the canal. The other 9 patients had satisfactory cosmetic results. All 11 patients were azoospermic. Biopsies were performed in Cases I, XI and XII.

Case II. In the left testis there was complete absence of spermatozoa and cell precursors. The Sertoli cells were prominent with hyaline thickening of the basement membrane of the tubules. On the right side the pattern was not so severe: there were some spermatids and spermatozoa with increased Sertoli cells.

In Case XI the right testicle showed complete atrophy of the spermatogonia with Sertoli cell replacement and on the left side only a quarter of the tubules examined had spermatogonia, the rest were lined by Sertoli cells. In Case XII the histological findings were failure of maturation on both sides.

Gross and Jewett (1956) reported 16 cases from the Boston Children's Hospital. Of these

12 who had the operation at 12 or under were fertile and 4 operated on between 10 and 12 were sterile. No mention is made in their paper of the size of the testes when adult life was reached. In their operation a wide retroperitoneal approach was used. The testes were gently restrained in the scrotum by a silk suture passed through the lower pole and connected to a rubber band secured to the thigh. All restraint was removed in six days. 15 other cases from the same hospital, operated on between 1900 and 1934, were collected by MacCollum (1935). In this group all the testes were in the canal or intra-abdominal and no scrotal fixation was employed. Of the 15, 11 were fertile, 2 of whom were operated on between 3 and 5, and the others between 7 and 11. Of the remaining 4 patients who were operated on at 11, 2 had azoospermia and 2 severe oligospermia. The combined figures from the Boston Children's Hospital show that 23/31 patients (77%) who had bilateral orchidopexy at 12 or earlier were fertile.

Sterility after bilateral orchidopexy can be due to:

(1) Intervention after irreversible changes have taken place.

(2) Faulty surgical technique producing injury to the blood vessels or the vas deferens.

(3) Constitutional defects in the testis.

There is much diversity of opinion as to the best time to operate. Romanis and Mitchiner (1952) do not advise operation before the 10th year and prefer to wait until the boy is 16. Handfield-Jones and Porritt (1957) see little reason for surgical treatment before puberty. Bishop (1949) holds that the testicle should be in the scrotum before the 12th birthday. In the United States the tendency is to operate much earlier and Campbell (1954) with a wide experience of pædiatric surgery prefers the age of 3. Those who prefer to operate at this time have been influenced by the work of Robinson and Engle (1954). They have shown that there is little histological difference between the undescended testis and the normally descended organ up to the age of 5 and then there is a definite slowing down of development. They believe that this retardation should be anticipated by operating before the age of 5 if no response is obtained to massive doses of gonadotrophin (4,000 units daily for three days).

In only 2 of the Hammersmith cases was operation performed at the 5th year. One patient was sterile and the other fertile. In the Boston series 2 were operated on between 3 and 5, and they were fertile, and the remainder were operated upon between the ages of 7 and 12. Presumably, therefore, the process of retardation is slow and may vary in degree and extent with each individual. This would explain the very satisfactory results in the cases operated on between 5 and 12. Another factor which cannot be ignored is that the surgeons at the Boston Children's Hospital were especially experienced in pædiatric surgery.

Apart from damage to the vas deferens and blood supply during the operation, thrombosis of the vessels can occur from forcible attempts to maintain the testis in the scrotum. No restraint was employed in the MacCollum series and a minimum in those reported by Gross and Jewett. Placing an ectopic testis in the scrotum is a relatively easy procedure, but with those in the canal or abdomen the operation can be extremely difficult. Patience and gentleness are required and it is wise to do one side at a time. Wide retroperitoneal access allows the vessels to be traced to their origin and restricting bands can be more easily visualized and divided. The distance to the scrotum can be shortened by causing the testicle to pass under and inside the deep epigastric vessels so that it emerges at the site of the external ring. If it cannot be brought down without tension the method recommended by Snyder and Chaffin (1955) may be used. The organ is secured at the lowest level possible and six months later a second attempt is made.

The undescended testis since Hunter's day has been regarded as constitutionally defective. Much of the evidence to uphold this view has been based on examination of undescended testes after the age of 5 (in Sohval's series (1954) the ages ranged between 7 months and 78 years). The changes noted might well be due to mal-descent alone. Some support for the view even though it is indirect, can be provided by examining normally descended testes in men with azoospermia and severe oligospermia. In a recent survey of 68 testicular biopsies (Carter, 1956) the following histological changes were observed: germinal aplasia, tubular fibrosis and maturation failure. In 33 (48·5%) the testes were normal in size and consistence, and in only 43 (63·5%) was there a history of infection, injury, hernia operations, and malposition. It is difficult to say what produced these disordered patterns—perhaps primary dysgenesis or some toxic or endocrinological factor, of which we are unaware. It is fair, I think, to assume that similar changes are likely to occur, perhaps more so, in undescended testes so that a certain proportion of cases will be sterile no matter how early and how well the operation has been performed.

*Conclusions.*—(1) As the undescended testes will not develop normally after the age of 5 it seems logical to suggest that they should be in the scrotum before that time. Presumably

the retardation of development, minimal at first, gradually becomes widespread and irreversible. This slow process would account for the results obtained by operation up to the age of 12. Ideally intervention should take place before the age of 5, or as soon as possible afterwards.

(2) A certain number of orchidopexies skilfully performed at the opportune time will fail because of testicular defects. These defects may be due to a primary congenital inadequacy, or to other unknown causes which influence spermatogenesis either before or after operation.

(3) A good cosmetic result after operation is no proof of fertility.

## REFERENCES


BISHOP, P. M. F. (1949) *Proc. R. Soc. Med.*, **42**, 655.
CAMPBELL, M. F. (1954) Urology. Philadelphia.
CARVER, J. H. (1956) Studies on Fertility. Oxford.
GROSS, R. E., and JEWETT, T. C. (1956) *J. Amer. med. Ass.*, **160**, 634.
HANDFIELD-JONES, R. M., and PORRITT, A. E. (1957) Essentials of Modern Surgery. Edinburgh.
MACCOLLUM, D. W. (1935) *Arch. Surg., Chicago*, **31**, 290.
ROBINSON, J. N., and ENGLE, E. T. (1954) *J. Urol.*, **71**, 726.
ROMANIS, W. H. C., and MITCHINER, P. H. (1952) Surgery. London.
SNYDER, W. H., Jr., and CHAFFIN, L. (1955) *J. Amer. med. Ass.*, **157**, 129.
SOHVAL, A. R. (1954) *J. Urol.*, **72**, 693.


## DISCUSSION

**Mr. Denis Browne** remarked on the advanced age at which Mr. Carver's cases had come to operation, an age at which many males were producing fertile spermatozoa. He suggested that this was because their advisers had "waited to see if they will come down", owing to incapacity to distinguish between true congenital deformities and normal variations in development. The diagnosis was a matter of understanding the anatomy and using the fingers to palpate; he considered hormones were quite useless for this purpose. When the diagnosis was made the rule held, here as elsewhere, that the earlier congenital deformities were corrected the better they developed afterwards. Unfortunately the lack of any agreement on easily demonstrable facts of anatomy made published work on the subject highly misleading.

**Professor Charles Wells** drew attention to the need for further information about the after-history in adult life of patients submitted to bilateral orchidopexy in childhood with particular reference to their success or otherwise in raising families.

**Mr. William S. Mack** said no one really had a clear idea about the question of fertility after orchidopexy since most workers had not followed up the cases that they had done. In addition it was more than likely that there was a difference in the prognosis between the true undescended testicle, which was often an immature organ, and the ectopic testicle, which, anatomically at least, was often well formed and healthy looking. He showed slides illustrating the immature histological picture in an undescended testicle in a boy of 12 as contrasted with the only slightly arrested development of an ectopic testicle in a boy of the same age. He had not yet been able to follow up all his patients but hoped in 10 or 12 years' time to be able to report further on a fairly large series of cases.

In the Fertility Clinic in Glasgow a survey had been made of an eight-year period. During this time 2,433 patients had been examined. 1,096 of them had shown some degree of subfertility. 108 patients in the series had evidence of undescended testicles, some of these patients having had surgical treatment and others having been left alone. Table I shows clearly the very poor outlook as regards fertility of patients with bilateral mal-descent, whether treated by operation or not, but, on reviewing the patients with unilateral descent, it was disconcerting to find that so many of them were sterile and this held good even when the descended testicle felt perfectly normal. In some cases a biopsy had been carried out on the apparently normal testicle and this had revealed a total absence of seminal cells. Obviously in many cases of undescended testicle there was a central fault which affected not merely the fertility of the mal-descended testicle but also the apparently normal descended testicle. In other words, no matter what form of treatment was applied in mal-descent of the testicle a certain fairly high percentage of cases would never become fertile.

TABLE I.

| | | Seminal fluid | | | |
|---|---|---|---|---|---|
| | No. | Normal | Impaired | Grossly impaired | Sperms absent |
| Unilateral. No operation.. | 37 | 7 | 8 | 12 | 10 |
| Unilateral with operation.. | 23 | 4 | 11 | 4 | 4 |
| Bilateral. No operation .. | 21 | 0 | 0 | 5 | 16 |
| Bilateral with operation .. | 27 | 0 | 2 | 3 | 22 |
| Totals | 108 | 11 | 21 | 24 | 52 |

**Mr. Carver,** in reply, said that waiting for undescended testicles to descend might be disappointing, for two reasons.

They might never come down, or if they did they might be non-fertile. Operation should be advised if there is no response to hormone therapy before the age of 5. There seemed to be no place for hormone therapy for unilateral maldescent. Statistics on the fertility of men whose testes descended at puberty were difficult to obtain.

# Bacteriæmia and Septicæmia after Urological Operations

By N. SLADE, M.B., F.R.C.S.
*Bristol*

THE familiar complications of urinary infection such as epididymitis and pyelonephritis are well recognized, and I wish to discuss a much less common but more serious complication—that of septicæmia which occasionally follows urinary sepsis.

Septicæmia, once dreaded in the pre-sulphonamide era, is becoming again more lethal due to the increased incidence of the antibiotic-resistant hospital organism. There has been a change of pattern in the responsible organism since 1937, for example, puerperal streptococcal septicæmia is now rare, on the other hand staphylococcal septicæmia has become relatively more important. The incidence of *B.coli* endocarditis in 1,000 cases of endocarditis analysed by Perry in 1936 was 0·8%, and there are only 4 examples recorded in some 5,000 autopsies performed by the department of Pathology in Bristol during the past twenty years—all 4 cases complicated operations involving the urinary tract.

In the past two years, however, there have been 9 cases of septicæmia diagnosed in our department; 2 of these were staphylococcal and the remainder Gram-negative septicæmias. 3 of these patients died.

The work of Gillespie (1956) on hospital cross-infection in relation to urological cases, has shown that most patients entering hospital with sterile urine acquire infection by cross-infection. The organism is often of the endemic hospital variety resistant to antibiotics and therefore the septicæmia is difficult to treat. In contrast, the patients with acute urinary tract symptoms at the time of admission to hospital are in general those with antibiotic-sensitive organisms (Kirby *et al.*, 1956). These patients, in our experience, do not usually get septicæmia.

In 1929, Scott reported 82 cases of blood-stream infection in urological cases from the Johns Hopkins Hospital, and a year later Barrington and Wright (1930) published their work on "Bacteriæmia following operations on the urethra".

In investigating the cause of "catheter fever" they confirmed that this was due to a bacteriæmia following the passage of instruments or removal of post-operative packs and hæmostatic bags, and that it was limited to cases in which a urinary infection already existed. They obtained positive blood cultures a few minutes after instrumentation and again shortly after the first micturition and concluded that the organisms may gain entrance at the time of trauma and also at the time urine is first passed along the traumatized urethra. The organisms isolated included *B. coli*, *proteus*, *pyocyaneus* and the staphylococcus.

Before I mention the research we have done, and why we did it, I would like to describe some of the 9 cases of septicæmia that have occurred in our department in the last two years. These cases fall into two well-defined groups. In the first there is an acute or subacute urinary infection following instrumentation or operation. This is followed several days later by the classical picture of septicæmia and is well illustrated by the case of Mr. H. J.—1 of 5 cases in the first group.

Mr. H. J., aged 65, a case of multiple bladder papillomata who had previously undergone some dozen cysto-diathermies without complication, was admitted five days after cysto-diathermy with a three-day history of rigors, pyrexia and diarrhœa. Soon after admission jaundice and petechial hæmorrhages were noticed. The urine yielded a heavy *Staph. aureus* infection and a blood culture showed a pure culture of *Staph. aureus*—of the same phage type (42 D.). This patient recovered on tetracycline, but nephrectomy was necessary later because of severe, chronic pyelonephritis.

Another case is that of a young man still in hospital. Reimplantation of the left ureter for stenosis of its lower end was complicated by urinary sepsis, pyelonephritis, ileus, and small bowel obstruction. His clinical condition remained grave with severe toxæmia and a month after his original operation, septicæmia was suspected when petechial hæmorrhages and diarrhœa were noted. A blood culture was taken, and oxytetracycline and later chloramphenicol given by intravenous route. There was a dramatic improvement in the first twenty-four hours and the blood culture yielded a growth of *B. pyocyaneus* with identical organisms in the urine.

In the second group of 4 cases, the illness was of much more rapid onset, bore a constant time relationship to the instrumentation or removal of the post-operative catheter, and had all the characteristics of "bacterial shock".

Our first case was a woman aged 44 who was admitted to our Department with anuria, twenty-four hours after a gynæcological repair operation in which there had been much bleeding. On admission, her general condition was fair; temperature 100° F., blood pressure 125/80. There was no urine in the bladder and the same evening a cystoscopy showed gross œdema of the bladder base and an extra-vesical mass, probably a hæmatoma, was felt between the bladder and vagina. Right ureterostomy was performed. The urine showed a *B. coli* infection and a vaginal swab yielded a coli-

form of the same type. In spite of antibiotics, during the next twelve hours her condition deteriorated rapidly and there was pyrexia of 103° F. The blood pressure dropped to 70/50 although there was no further blood loss. The patient died just forty-eight hours after the first, that is, the gynæcological operation, and autopsy showed obstruction of both lower ureters by the pelvic haematoma. A blood culture taken before death yielded a pure growth of *B. coli* of the same sensitivity pattern as that of the urine.

A very short time after this I was called to the ward to see a patient who had collapsed a few hours after removal of his catheter. He had undergone transurethral resection of multiple papillomata and hypertrophied bladder neck two days previously, and had passed urine just before his collapse with great difficulty and much straining due to partial obstruction with blood clot and debris.

I found him ashen grey, almost unconscious and with a blood pressure of 70/40. As there was some lower abdominal tenderness I thought at first of an extravasation of urine due to a ruptured bladder, also of some catastrophe such as coronary thrombosis or large pulmonary embolus. A little later there were rigors and a pyrexia of 103° F., and because of the similarity to the previous case a blood culture was put up, and parenteral antibiotics given. Intramuscular chloramphenicol and intravenous oxytetracycline were used as the urine specimen of the previous day showed a *B. coli/pyocyaneus* infection. The blood culture the following day yielded a growth of *B. coli* with the same sensitivity pattern and another Gram-negative bacillus which did not subculture. The clinical condition remained grave for twenty-four hours with sustained hypotension, but in three days he had recovered.

Yet a third case occurred a few months later. This followed a retropubic prostatectomy and symptoms commenced three hours after catheter removal. Again a medical emergency was suspected and in this case a medical opinion was sought—the physician suspected massive pulmonary embolism, but in view of our past experiences blood cultures were taken and intramuscular chloramphenicol given. The temperature had by this time risen to 103° F. and the urine showed a proteus infection. There was a dramatic improvement overnight and the following day both culture bottles yielded a pure growth of proteus.

4 cases then presented as "bacterial shock". This condition has received more attention in the United States. In a paper analysing 38 cases Ezzo and Knight (1957) define it as a septicæmia in which there is acute circulatory failure due to liberation of endotoxins, and there must be a positive blood culture and hypotension of 85 mm.Hg systolic or less. 23 cases were due to Gram-negative organisms, and 16 of the 38 cases followed operation on the urinary tract.

We considered that the apparent association of the catheter removal, or first micturition, with the onset of symptoms in the 4 cases of bacterial shock merited clinical investigation. We knew from Barrington's work that a transitory bacteriæmia often followed instrumentation, and it was one step farther to postulate that something similar occurred when withdrawing a catheter along an inflamed mucosal tube in the presence of infected urine.

We have now completed investigation on a total of 50 patients involving some 200 blood cultures. In the first series blood cultures were taken from 19 patients shortly after catheter removal following operations, both open and transurethral, on the prostate and bladder. A control blood culture was taken the following day, and the first urine voided after catheter removal was cultured for organisms. This urine was infected in all cases, although in 14 the pre-operative specimen was sterile.

In the first 9 cases I took the blood sample approximately one hour after catheter removal and these samples remained sterile. The interval was obviously too long and in the remaining 10 cases the blood sample was taken five minutes after catheter removal and in 5 cases we obtained positive blood cultures. The 19 control blood cultures remained sterile.

TABLE I.—1ST SERIES—19 CASES. 5 POSITIVE BLOOD CULTURES

| Case No. | Blood culture | Urine culture |
|---|---|---|
| X | Mixed coliforms | Mixed coliforms |
| XI | *Staph. albus* | *B. coli* |
| | Coag. —ve in 11 days | Proteus |
| XII | *Strep. fæcalis* | *Strep. fæcalis* |
| XIII | *Staph. albus* | Coliforms |
| | Non-hæm. strep. | |
| XVI | *Staph. albus* | Proteus |
| | Coag. —ve | Coliforms |

You will note that in 2 cases the organism isolated in the blood culture was also present in the urine. In 3 cases we were unable to culture similar organisms in the urine, and in 1 of them the blood culture yielded a very scanty growth after eleven days' incubation, and could have been a contaminant. This pilot series showed therefore that a bacteriæmia could occur after catheter removal, and encouraged us to carry out a fully controlled series.

In the second series of 15 patients, we cultured the urine pre-operatively, immediately

before catheter removal, and the first post-catheter micturition specimen. Three blood cultures were taken:

Sample 1. Immediately prior to catheter removal.
Sample 2. Two to three minutes after catheter removal.
Sample 3. Approximately fifteen minutes after catheter removal (Fig. 1).

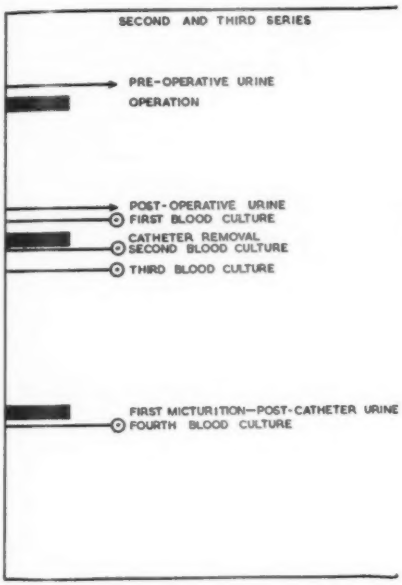



FIG. 1.—Illustrating the time relationships of the various blood cultures and urine samples to the operation and catheter removal.

TABLE II.—2ND SERIES—15 CASES.
4 POSITIVE BLOOD CULTURES

7 Cases—Post-operative Urine Sterile and all Blood Cultures Sterile

| | Case No. | Blood culture | Urine culture |
|---|---|---|---|
| In 8 infected cases | I | Pyocyaneus *Strep. fæcalis* | Pyocyaneus *Strep. fæcalis* |
| | V | *Staph. albus* | *Staph. albus* Coliforms |
| | XIV | *Staph. albus* | *Staph. albus* *Strep. fæcalis* |
| | XII | Atypical Gram-negative bacillus | Atypical Gram-negative bacillus |

In all cases the first and the third blood specimens remained sterile. In 7 cases in which the urine immediately prior to catheter removal was sterile, the second blood culture was sterile, but of the remaining 8 infected cases 3 showed organisms in the blood culture which linked up with those in the urine; and in 1 other case in which the catheter fell out and was replaced shortly after, a blood culture, taken because the patient had a rigor, showed a Gram-negative bacteriæmia corresponding to the urinary infection.

In our third series we took similar urine specimens and blood samples, not only in relation to the catheter removal but, where possible, immediately after the first natural micturition. These latter samples were, for obvious reasons, more difficult to obtain and so far all have remained sterile. Of the 16 cases in the third series, 11 had infected urine at the time of catheter removal, and in only 1 case was there a positive blood culture—two organisms, *Staph. albus* and *Staph. aureus*, were isolated from both blood and urine. The results in the three series are summarized in Table III.

TABLE III.—RESULTS IN 50 CASES

| Urine when catheter removed | No. | Results |
|---|---|---|
| Sterile | 12 cases | All blood cultures were sterile |
| Infected | 38 cases | 28 remained sterile<br>In 10 *cases* positive blood culture 2–10 min. after catheter removal |

We had hoped to demonstrate a bacteriæmia at the first micturition after catheter removal or even after straining to pass urine or straining at stool in the first few hours; so far, however, we have been unsuccessful, but I am convinced that a bacteriæmia can and does occur at this time.

We have also carried out a short series of blood cultures after instrumentation alone — by way of confirming Barrington's work. Table IV shows the result.

TABLE IV.—BLOOD CULTURES AFTER URETHRAL INSTRUMENTATION—11 CASES

| | | |
|---|---|---|
| Urine sterile | 3 cases | All blood cultures sterile |
| Urine infected | 8 cases | Blood cultures positive in 2 cases and similar organism in the urine (*B. coli*, *Strep. fæcalis*) |

## CONCLUSIONS

We have demonstrated that, of 38 patients in whom the urine was infected at the time of catheter removal, a transitory bacteriæmia occurred in 10 and in 7 an organism with the same biochemical and/or sensitivity pattern was found in the urine. The organism appeared a few minutes after catheter removal and disappeared in fifteen minutes.

We believe that this is the mechanism and portal of entry by which a septicæmia can occur after urological operations, and that the incidence may be much greater than is thought because bacterial shock may cause death so rapidly that a confident clinical diagnosis of massive pulmonary embolism is made. However, the unusual combination of hypotension and pyrexia should lead one to think of bacterial shock.

The classical picture of septicæmia may not be clinically distinguished from a severe urinary infection, but the strangely apathetic, pallid, sometimes cyanosed facial appearance in a patient who is known to have pyelonephritis may make one think of a coliform infection.

We have found intravenous oxytetracycline and chloramphenicol the most useful antibiotics, and prompt and energetic therapeutic measures are a matter of profound urgency.

Finally, this is just another reason for improving our methods of prevention of post-operative urinary infection, and our findings give further support to the theory of hæmatogenous origin of the so-called ascending pyelonephritis.

I would like to associate with this work the name of Mr. K. B. Linton, who has done most of the bacteriology. Also I wish to thank Mr. Ashton Miller and Dr. W. A. Gillespie for encouragement and help in preparation of the paper.

## REFERENCES

BARRINGTON, F. J. F., and WRIGHT, H. D. (1930) *J. Path. Bact.*, **33**, 871.
EZZO, J. A., and KNIGHT, W. A., Jr. (1957) *Arch. intern. Med.*, **99**, 701.
GILLESPIE, W. A. (1956) *Proc. R. Soc. Med.*, **49**, 1045.
KIRBY, W. M. M., CORPRON, D. O., and TANNER, D. C. (1956) *J. Amer. med. Ass.*, **162**, 1.
SCOTT, W. W. (1929) *J. Urol.*, **21**, 527.

[*February* 27, 1958]

THE following Specimens were shown:

**Reticulo-sarcoma of Testis.**—Mr. G. LUMB (for Professor R. MILNES WALKER).

**Reticulo-sarcoma of Testis.**—Mr. G. LUMB (for Mr. S. GLASER).

**Testicular Tumour with Unusual Clinical Features.**—Dr. R. C. B. PUGH and Mr. H. K. VERNON.

**Infarction of the Testis.**—Mr. N. SLADE (for Mr. ASHTON MILLER).

**Sarcoma of Penis.**—Mr. E. W. RICHES.

**Eosinophilic or Allergic Granuloma of Prostate.**—Dr. J. H. O. EARLE.

**Neurogenic Bladder. Cauda Equina Tumour. Ependymoma.**—Mr. D. TOOMS (for Mr. H. G. HANLEY).

**Uretero-colic Anastomosis, showing Late Regression of Post-operative Hydronephrosis.**—Mr. W. B. WATERFALL.

**Bilateral Renal Filling Defects.**—Mr. N. SLADE (for Mr. J. P. MITCHELL).

**Carcinoma of Urachus.**—Mr. ALEX. ROCHE.

# Section of Pathology

President—Professor J. W. S. BLACKLOCK, M.D.

[*November* 19, 1957]

## Diabetes Insipidus: The Contribution of Histochemical and Isotope Techniques to the Investigation of Its Pathogenesis

By J. C. SLOPER, M.D.

*London*

THE study of diabetes insipidus has been greatly impeded by the controversy which has persisted, at least until recently, concerning the identity of the cells responsible for the elaboration of the posterior pituitary principles. It is the purpose of this paper briefly to review the evidence which points to the secretion of these substances by neurones, and to consider the implications of this theory in the study of the pathogenesis of diabetes insipidus. Newer cytochemical techniques are proving of great value in the investigation of these problems.

### THE IDENTITY OF THE CELLS SECRETING THE POSTERIOR PITUITARY PRINCIPLES

The secretion of the posterior pituitary principles has been attributed at various times to the interstitial cells of the neurohypophysis, to its nerve-fibres and to its epithelial sheath. In recent years the secretory role of the latter (Fig. 1) has been little supported. Thus,

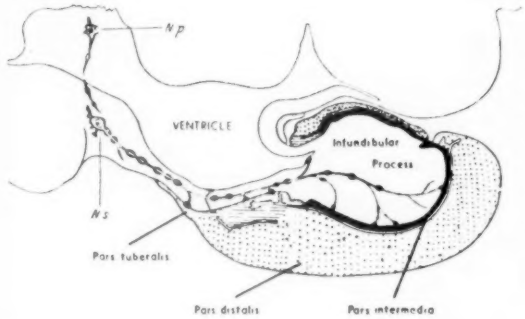



FIG. 1.—Diagram (modified from Bargmann, 1951) of sagittal section through hypothalamus and pituitary of a dog. Note glandular sheath (pars tuberalis and pars intermedia) of neurohypophysis (median eminence: infundibular stem: infundibular process). "Pituicytes" are confined to the neurohypophysis. The main innervation of this region is derived from the supraoptic (N.S.) and paraventricular (N.P.) nuclei, which lie in the hypothalamus.

pharmacological investigations in species which lack a pars intermedia (Geiling and Oldham, 1937) make it unlikely that this is the source of the vasopressor-antidiuretic principle; again, pars tuberalis, which partially ensheathes the infundibular stem (the pituitary stalk) has rarely been attributed with this role (Trendelenburg, 1928; Biggart, 1936). Consequently, if any single structure is the source of the antidiuretic principle, it is probably represented either by the nerves or by the interstitial cells of the neurohypophysis. Direct evidence from tissue cultures is inconclusive (Hild, 1954). The evidence is therefore indirect, and centres on the identification of specific secretory structures in the regions from which posterior pituitary principles can be recovered. As many as five categories of *interstitial* cell can be distinguished with the silver carbonate technique originally recommended by Bucy (1930), namely adeno-, fibro-, reticulo-, and micro-pituicytes (Romeis, 1940), and microglial cells (Vazquez-Lopez, 1942). It is nevertheless held that "pituicytes" thus demonstrated are confined to the neurohypophysis (Weaver and Bucy, 1940), that is, the infundibular process (pars nervosa), infundibular stem (pituitary stalk) and median eminence (the tuber cinereum). It follows that pituicytes cannot be the immediate source of those substances with posterior pituitary activity which have been recovered from the supraoptic and paraventricular nuclear regions of the hypothalamus (Hild and Zetler, 1953).

These nuclear regions contain the cell-bodies of the neurones which innervate the neurohypophysis, cells to which Scharrer and Scharrer (*see* review, 1940), had long attributed an endocrine function. The clue to this function was provided by Gaupp (1944), but it is to Bargmann and his school (*see* review, 1954), that the definitive work in this field must be

attributed. It was shown that a deeply staining chrome-alum hæmatoxyphil (CAH) "neurosecretory" material both filled the infundibular process of the pituitary and extended down into it along the tractus hypophyseus from the supraoptic and paraventricular nuclei. This material was depleted from the pituitary by osmotic stress; it accumulated above lesions in the pituitary stalk; and throughout its distribution substances with posterior pituitary activity could be recovered. It was therefore suggested that hormone and "neurosecretory" colloid were formed in the nuclear regions, passed down the tractus hypophyseus, and were stored and released from the posterior pituitary (Bargmann, 1951; Hild and Zetler, 1951; Bargmann and Scharrer, 1951).

This colloid presented an interesting histochemical problem; for the selectivity with which it could be stained suggested the presence of some substance peculiar to the region, or at least present there in higher concentration than in the neighbouring brain. Schiebler (1951, 1952) supposed that it represented a glyco-lipo-protein bearer-substance for posterior pituitary principle, insisting that the colloid, unlike the active principle, was removed from the unfixed pituitary by lipid-solvents. Like Gersh (*see* Wingstrand, 1953) who had earlier claimed that the Herring bodies of the posterior pituitary were histological artefacts, Schiebler attempted to demonstrate colloid in tissues which had not at any stage of their processing been exposed to formalin. If, however, the pituitary, after lipid-extraction, is fixed in formalin, then colloid can readily be demonstrated. Further, throughout the distribution of Bargmann's CAH "neurosecretory" material there is a substance which reacts far more strongly than the adjacent brain with histochemical techniques for protein-bound cystine (Sloper, 1954, 1955), an amino acid also identified in this region by Barrnett (1954). On histochemical grounds, therefore, it seems likely that there is a protein constituent of "neurosecretory" material, which is present both in hypothalamus and pituitary, and which is rich in cystine. This substance could well represent posterior pituitary principle, particularly if the latter is present in the tissues as a complex of Van Dyke protein and Du Vigneaud's octapeptides (Acher, 1958), since both contain a high proportion of cystine.

In the median eminence and infundibular stem, there is very little "neurosecretory" material and few fibres pass close to capillaries. The opposite is the case in the infundibular process, where the terminal arborizations of the nerves of the tractus hypophyseus ramify in interwoven lobules, ending on the walls of capillaries. The architecture of these lobules has been clarified by Palay (1955, 1957), whose observations amplify those of Romeis (1940), Vazquez-Lopez (1942), and Bodian (1951). From the study of electron-photomicrographs he concluded that "neurosecretory" material is enclosed within nerve fibres and their terminal expansions. These expansions, interdigitating with the processes of pituicytes, which he regards as supportive, end adjacent to capillaries. "Neurosecretory" material he identified with certain vesicles (the granules of Green and Van Breemen, 1955). These are peculiar to the region, and like antidiuretic principle and cystine-rich "neurosecretory" material, are depleted by osmotic stress. The reactivity of the contents of Palay's vesicles with osmium tetroxide does not preclude their protein nature (Bahr, 1954), and it would be of interest to attempt to demonstrate them in electron-photomicrographs with reagents capable of demonstrating the sulphydryl groups of reduced cystine (Bahr and Moberger, 1954).

To summarize, we have to consider some three categories of particle. First, there is the Van Dyke protein, to which, in the tissues, Du Vigneaud's octapeptides may be attached (Acher, 1958). This protein has a molecular weight of 30,000 and probably a diameter of between 0·001 and 0·01 $\mu$. Second, there is Palay's vesicle, which is about 0·1 $\mu$ in diameter and appears in electron-photomicrographs to contain dense, perhaps particulate, inclusions. Third, we have the cystine-rich granule, some 2 $\mu$ in diameter, which is visible with the light microscope. It is possible that protein, particulate inclusion, and granule all represent posterior pituitary principle. It is suggested that the synthesis, transport, storage and release of these particles is the property of the cytoplasm and axoplasm of "neurosecretory" cells (Fig. 2). An obvious compromise between the concepts of central (Bargmann) and peripheral (Bodian) synthesis is to suppose that the entire axoplasm is capable of synthesis, but that transference of posterior pituitary principle into the blood-stream is normally confined to the infundibular process, and perhaps also to the infundibular stem and median eminence.

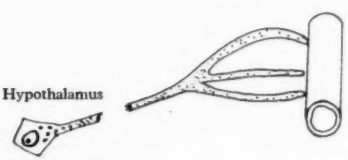



FIG. 2.—Diagram illustrating concept of neurosecretion. Posterior pituitary principle and "neurosecretory" material are held to be formed in the cytoplasm of the cell-bodies of neurones, and perhaps also in their axoplasm; to flow down the axones of these neurones in the tractus hypophyseus; and to be stored in, and released from, the neurohypophysis.

### Pathological Considerations

Necropsies on cases of diabetes insipidus are infrequent and there has been little opportunity to study in such cases the distribution of "neurosecretory" material. The distribution of the latter should, in pathological tissues, be investigated by histochemical techniques rather than by the chrome-hæmatoxylin and aldehyde-fuchsin methods originally introduced for this purpose. Of these techniques, the most convenient depends upon acid-oxidation followed by the use of a basic dye at a very low pH (Adams and Sloper, 1956). This technique allows the differentiation of cystine-rich "neurosecretory" material from those neuronal inclusions which lack such cystine-rich material, but which are nevertheless stained by the chrome-hæmatoxylin and aldehyde-fuchsin methods. The latter, by reason of this lack of specificity, are also of limited value in the investigation of the local changes which follow injury to the pituitary stalk. Histochemical techniques serve here to differentiate cystine-rich material from necrotic debris. Such techniques are also, by reason of their selectivity, of great topographical value. This applies particularly to the identification of the fibres of the tractus hypophyseus. The somewhat devious and caudal course of some of the nerve fibres derived from the paraventricular nuclei has only been recognized since methods were introduced for the demonstration of "neurosecretory" material.

The topographical value of these techniques would alone recommend their use in the investigation of the morbid anatomy of diabetes insipidus. Two varieties of this disease have been recognized, the one primary or idiopathic, the other secondary or symptomatic. The diagnosis of the *idiopathic* form has usually been made on clinical grounds by the exclusion of those conditions which are either known to cause the disease, or are of possible ætiological significance (*see* reviews by Staemmler, 1932; Blotner, 1950; Orthner, 1955; Rodeck, 1955). Pathological information is scanty, and it is not surprising that the proportion of cases included in this idiopathic category has varied greatly. Blotner (1937) provided incomplete pathological data on two such cases, while Gaupp (1941) described in detail the changes in a woman who suffered from the familial form of the disease. Some familial cases are resistant to Pitressin (Forssmann, 1945) and have been termed "nephrogenic"; in such cases the nature of the renal lesion is obscure (Kirman *et al.*, 1956), and I have found no adequate description of the hypothalamo-hypophyseal system.

More is known of the pathology of *symptomatic* diabetes insipidus. The characteristic lesion is a neoplasm or granuloma, interrupting the tractus hypophyseus, and in many instances causing extensive damage to the hypothalamus or pituitary. There are, however, other cases where the extent and nature of the injury are still obscure. For example, in post-encephalitic diabetes insipidus histological damage to hypothalamus and pituitary may be negligible (Croll, 1930; and *see* Orthner, 1955). Again, I have found no description of the pathological changes which occur in cases where the disease has been attributed to psychogenic disturbance, and only one description (Henzi, 1952) of these changes in a case where the condition was due to head injury.

Of these various forms of the disease some examples of symptomatic diabetes insipidus, in which there were destructive lesions interrupting the tractus hypophyseus, have already been investigated with techniques for the demonstration of "neurosecretory" material (Weicksel and Cain, 1952; Drager and Russell, 1954; Rothballer and Dugger, 1955). In every case, a marked diminution of the number of "neurosecretory" cells was observed. The more interesting cases, however, are likely to be those in which little or no damage to the hypothalamo-hypophyseal system has been reported. In such cases, it is possible that the essential lesion lies outside the system, involving for example the paraventricular nuclei of the thalamus, the integrity of which is essential in the dog for the function of the osmoreceptors (Jewell and Verney, 1957). Alternatively, it is possible that the study of the distribution of "neurosecretory" material may reveal cases in which there is a defect in the formation, transport, storage, or release of this material. Some such dysfunction may indeed account for the apparent absence of damage to the nuclear regions in a case of diabetes insipidus recently described by Dingman *et al.* (1957).

### The Pathogenesis of the Disease

The fundamental problem is the reaction of the "neurosecretory" cell to injury. Despite the early and detailed experimental investigations in this field (e.g. Kary, 1924; Mogilnitzky, 1928) the information which has been obtained with conventional histological techniques is limited. The major difficulty is the pseudopathological appearance of the normal "neurosecretory" cell. Not one of such features as gross cytoplasmic vacuolation, the segregation of Nissl substance and nucleus to the periphery of the cell-body, or the loss of Nissl substance, is evidence of irreversible damage (*see* Bargmann, 1954). Moreover, as Tello (1912) stressed, the nerve fibres in the pituitary normally exhibit features indicative elsewhere in the nervous system of regeneration and degeneration, features which in terms of the "neurosecretory" hypothesis merely indicate the distortion of nerve terminals by "neurosecretory" material.

attributed. It was shown that a deeply staining chrome-alum hæmatoxyphil (CAH) "neurosecretory" material both filled the infundibular process of the pituitary and extended down into it along the tractus hypophyseus from the supraoptic and paraventricular nuclei. This material was depleted from the pituitary by osmotic stress; it accumulated above lesions in the pituitary stalk; and throughout its distribution substances with posterior pituitary activity could be recovered. It was therefore suggested that hormone and "neurosecretory" colloid were formed in the nuclear regions, passed down the tractus hypophyseus, and were stored and released from the posterior pituitary (Bargmann, 1951; Hild and Zetler, 1951; Bargmann and Scharrer, 1951).

This colloid presented an interesting histochemical problem; for the selectivity with which it could be stained suggested the presence of some substance peculiar to the region, or at least present there in higher concentration than in the neighbouring brain. Schiebler (1951, 1952) supposed that it represented a glyco-lipo-protein bearer-substance for posterior pituitary principle, insisting that the colloid, unlike the active principle, was removed from the unfixed pituitary by lipid-solvents. Like Gersh (*see* Wingstrand, 1953) who had earlier claimed that the Herring bodies of the posterior pituitary were histological artefacts, Schiebler attempted to demonstrate colloid in tissues which had not at any stage of their processing been exposed to formalin. If, however, the pituitary, after lipid-extraction, is fixed in formalin, then colloid can readily be demonstrated. Further, throughout the distribution of Bargmann's CAH "neurosecretory" material there is a substance which reacts far more strongly than the adjacent brain with histochemical techniques for protein-bound cystine (Sloper, 1954, 1955), an amino acid also identified in this region by Barrnett (1954). On histochemical grounds, therefore, it seems likely that there is a protein constituent of "neurosecretory" material, which is present both in hypothalamus and pituitary, and which is rich in cystine. This substance could well represent posterior pituitary principle, particularly if the latter is present in the tissues as a complex of Van Dyke protein and Du Vigneaud's octapeptides (Acher, 1958), since both contain a high proportion of cystine.

In the median eminence and infundibular stem, there is very little "neurosecretory" material and few fibres pass close to capillaries. The opposite is the case in the infundibular process, where the terminal arborizations of the nerves of the tractus hypophyseus ramify in interwoven lobules, ending on the walls of capillaries. The architecture of these lobules has been clarified by Palay (1955, 1957), whose observations amplify those of Romeis (1940), Vazquez-Lopez (1942), and Bodian (1951). From the study of electron-photomicrographs he concluded that "neurosecretory" material is enclosed within nerve fibres and their terminal expansions. These expansions, interdigitating with the processes of pituicytes, which he regards as supportive, end adjacent to capillaries. "Neurosecretory" material he identified with certain vesicles (the granules of Green and Van Breemen, 1955). These are peculiar to the region, and like antidiuretic principle and cystine-rich "neurosecretory" material, are depleted by osmotic stress. The reactivity of the contents of Palay's vesicles with osmium tetroxide does not preclude their protein nature (Bahr, 1954), and it would be of interest to attempt to demonstrate them in electron-photomicrographs with reagents capable of demonstrating the sulphydryl groups of reduced cystine (Bahr and Moberger, 1954).

To summarize, we have to consider some three categories of particle. First, there is the Van Dyke protein, to which, in the tissues, Du Vigneaud's octapeptides may be attached (Acher, 1958). This protein has a molecular weight of 30,000 and probably a diameter of between 0·001 and 0·01 $\mu$. Second, there is Palay's vesicle, which is about 0·1 $\mu$ in diameter and appears in electron-photomicrographs to contain dense, perhaps particulate, inclusions. Third, we have the cystine-rich granule, some 2 $\mu$ in diameter, which is visible with the light microscope. It is possible that protein, particulate inclusion, and granule all represent posterior pituitary principle. It is suggested that the synthesis, transport, storage and release of these particles is the property of the cytoplasm and axoplasm of "neurosecretory" cells (Fig. 2). An obvious compromise between the concepts of central (Bargmann) and peripheral (Bodian) synthesis is to suppose that the entire axoplasm is capable of synthesis, but that transference of posterior pituitary principle into the blood-stream is normally confined to the infundibular process, and perhaps also to the infundibular stem and median eminence.

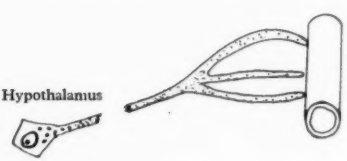



FIG. 2.—Diagram illustrating concept of neurosecretion. Posterior pituitary principle and "neurosecretory" material are held to be formed in the cytoplasm of the cell-bodies of neurones, and perhaps also in their axoplasm; to flow down the axones of these neurones in the tractus hypophyseus; and to be stored in, and released from, the neurohypophysis.

### Pathological Considerations

Necropsies on cases of diabetes insipidus are infrequent and there has been little opportunity to study in such cases the distribution of "neurosecretory" material. The distribution of the latter should, in pathological tissues, be investigated by histochemical techniques rather than by the chrome-hæmatoxylin and aldehyde-fuchsin methods originally introduced for this purpose. Of these techniques, the most convenient depends upon acid-oxidation followed by the use of a basic dye at a very low pH (Adams and Sloper, 1956). This technique allows the differentiation of cystine-rich "neurosecretory" material from those neuronal inclusions which lack such cystine-rich material, but which are nevertheless stained by the chrome-hæmatoxylin and aldehyde-fuchsin methods. The latter, by reason of this lack of specificity, are also of limited value in the investigation of the local changes which follow injury to the pituitary stalk. Histochemical techniques serve here to differentiate cystine-rich material from necrotic debris. Such techniques are also, by reason of their selectivity, of great topographical value. This applies particularly to the identification of the fibres of the tractus hypophyseus. The somewhat devious and caudal course of some of the nerve fibres derived from the paraventricular nuclei has only been recognized since methods were introduced for the demonstration of "neurosecretory" material.

The topographical value of these techniques would alone recommend their use in the investigation of the morbid anatomy of diabetes insipidus. Two varieties of this disease have been recognized, the one primary or idiopathic, the other secondary or symptomatic. The diagnosis of the *idiopathic* form has usually been made on clinical grounds by the exclusion of those conditions which are either known to cause the disease, or are of possible ætiological significance (*see* reviews by Staemmler, 1932; Blotner, 1950; Orthner, 1955; Rodeck, 1955). Pathological information is scanty, and it is not surprising that the proportion of cases included in this idiopathic category has varied greatly. Blotner (1937) provided incomplete pathological data on two such cases, while Gaupp (1941) described in detail the changes in a woman who suffered from the familial form of the disease. Some familial cases are resistant to Pitressin (Forssmann, 1945) and have been termed "nephrogenic"; in such cases the nature of the renal lesion is obscure (Kirman *et al.*, 1956), and I have found no adequate description of the hypothalamo-hypophyseal system.

More is known of the pathology of *symptomatic* diabetes insipidus. The characteristic lesion is a neoplasm or granuloma, interrupting the tractus hypophyseus, and in many instances causing extensive damage to the hypothalamus or pituitary. There are, however, other cases where the extent and nature of the injury are still obscure. For example, in post-encephalitic diabetes insipidus histological damage to hypothalamus and pituitary may be negligible (Croll, 1930; and *see* Orthner, 1955). Again, I have found no description of the pathological changes which occur in cases where the disease has been attributed to psychogenic disturbance, and only one description (Henzi, 1952) of these changes in a case where the condition was due to head injury.

Of these various forms of the disease some examples of symptomatic diabetes insipidus, in which there were destructive lesions interrupting the tractus hypophyseus, have already been investigated with techniques for the demonstration of "neurosecretory" material (Weicksel and Cain, 1952; Drager and Russell, 1954; Rothballer and Dugger, 1955). In every case, a marked diminution of the number of "neurosecretory" cells was observed. The more interesting cases, however, are likely to be those in which little or no damage to the hypothalamo-hypophyseal system has been reported. In such cases, it is possible that the essential lesion lies outside the system, involving for example the paraventricular nuclei of the thalamus, the integrity of which is essential in the dog for the function of the osmoreceptors (Jewell and Verney, 1957). Alternatively, it is possible that the study of the distribution of "neurosecretory" material may reveal cases in which there is a defect in the formation, transport, storage, or release of this material. Some such dysfunction may indeed account for the apparent absence of damage to the nuclear regions in a case of diabetes insipidus recently described by Dingman *et al.* (1957).

### The Pathogenesis of the Disease

The fundamental problem is the reaction of the "neurosecretory" cell to injury. Despite the early and detailed experimental investigations in this field (e.g. Kary, 1924; Mogilnitzky, 1928) the information which has been obtained with conventional histological techniques is limited. The major difficulty is the pseudopathological appearance of the normal "neurosecretory" cell. Not one of such features as gross cytoplasmic vacuolation, the segregation of Nissl substance and nucleus to the periphery of the cell-body, or the loss of Nissl substance, is evidence of irreversible damage (*see* Bargmann, 1954). Moreover, as Tello (1912) stressed, the nerve fibres in the pituitary normally exhibit features indicative elsewhere in the nervous system of regeneration and degeneration, features which in terms of the "neurosecretory" hypothesis merely indicate the distortion of nerve terminals by "neurosecretory" material.

Unequivocal evidence of degeneration, that is degeneration characterized by cytolysis, karyorrhexis and karyolysis, does not, in fact, appear in the human until between seventeen and forty-two days after injury to the pituitary stalk. To investigate the susceptibility of the "neurosecretory" cell to various forms of injury it would clearly be advantageous to have histological criteria indicative of irreversible damage at an earlier stage. A change which can be interpreted in this way is the retrograde accumulation of "neurosecretory" material in the axone and the cell-body of many "neurosecretory" cells following, for example, hypophysectomy in the rat (Stutinsky, 1951). In a human, where death had occurred ten days after hypophysectomy for the relief of malignant disease, such changes were very marked (Sloper and Adams, 1956), and it seems that at least a proportion of the neurones thus affected were undergoing irreversible degeneration. This interpretation must nevertheless be made with caution, for conspicuous aggregations of "neurosecretory" material have been observed in the intrahypothalamic portion of the tractus hypophyseus in the overhydrated dog (Andersson and Jewell, 1957). In such animals the accumulation could be a reversible change, indicative of a transient disturbance of the axonal transport of the "neurosecretory" material.

Early pathological changes in "neurosecretory" cells can be further investigated in two ways, the first involving the study of those enzymes which are conspicuous in the cytoplasm of the neurones of the supraoptic and paraventricular nuclei. These include acid phosphatase and various esterases (Eränkö, 1951; Gomori and Chessick, 1953; Sloper, 1955). Their function is unknown, but it has been shown that certain esterases are markedly affected by osmotic stress (Pepler and Pearse, 1957). A property of the "neurosecretory" cell which is easier to measure is its uptake of the isotope sulphur 35, injected intracisternally in the form of labelled cysteine (Arnott and Sloper, 1958). Sulphur 35 accumulates first in the nuclear region, and later in the infundibular process. We are hoping to use this property of the hypothalamo-hypophyseal system as a means of studying its susceptibility to injury, and in particular to injury by ionizing radiations (Arnold, 1955).

A second problem under investigation is the late effect of injury on the "neurosecretory" cell. Shortly after section of the pituitary stalk there is a local accumulation of CAH material, which, like that in the nerve fibres, is rich in cystine. This phenomenon has been observed in many species including man. In the rat the accumulation appears either to persist or to reform, and a month after the injury the median eminence, now full of "neurosecretory" material, resembles the normal posterior pituitary (Stutinsky, 1951). The histochemical properties of these persistent accumulations have yet to be investigated. Such accumulations are not depleted by osmotic stress quite as readily as the "neurosecretory" material stored in the normal infundibular process (Billenstien and Leveque, 1955). Their development can be explained in two ways. Fibres normally ending in the median eminence may take over the function of fibres destroyed by section of the pituitary stalk. Alternatively, injured fibres may be capable of regeneration, and of making contact with vessels in the median eminence. These alternatives have also to be considered in the interpretation of the changes which occur in the human median eminence following surgical injury (Sloper and Adams, 1956). In particular, the possibility of neuronal regeneration should not be dismissed (Tello, 1912; Bodian and Maren, 1951; Diepen *et al.*, 1954) despite the fact that regeneration is held not to occur in the central nervous system. If substantiated it would explain a phenomenon stressed by many workers (*see* Porter and Miller, 1948), namely the spontaneous recovery of many cases of traumatic diabetes insipidus.

## Conclusion

An account has been given of recent investigations into the pathogenesis of diabetes insipidus. These have been based on the hypothesis—still disputed, although no attempt has been made here to discuss its more controversial aspects—that antidiuretic hormone is formed not by "pituicytes" but by certain secretory neurones of the hypothalamo-neurohypophyseal system. It follows from this hypothesis that the essential abnormality in diabetes insipidus is the destruction or dysfunction of these neurones, and it is with their reaction to stress and to injury that we have been concerned. An outline has been given of the application of certain newer histochemical techniques to their investigation both in the experimental animal and in human material. Since few cases of diabetes insipidus come to necropsy, and since our understanding of its patholgy is still incomplete, it would be of the greatest value if material from such cases could be investigated by the techniques now available.

## References

Acher, R. (1958) Proc. 2nd Symposium on Neurosecretion (Lund, 1957). Heidelberg (in press).
Adams, C. W. M., and Sloper, J. C. (1956) *J. Endocrin.*, **13**, 221.
Andersson, B., and Jewell, P. A. (1957) *J. Endocrin.*, **15**, 332.
Arnold, A. (1955) *J. clin. Endocrin.*, **14**, 859.
Arnott, D. J., and Sloper, J. C. (1958) (Proc.) *J. Anat., Lond.* In press.

BAHR, G. F. (1954) *Exp. Cell Res.*, **7**, 457.
——, and MOBERGER, G. (1954) *Exp. Cell Res.*, **6**, 506.
BARGMANN, W. (1951) *Med. Mschr., Stuttgart*, **5**, 466.
—— (1954) Das Zwischenhirn-hypophysensystem. Berlin.
——, and SCHARRER, E. (1951) *Amer. Scient.*, **39**, 255.
BARRNETT, R. J. (1954) *Endocrinology*, **55**, 484.
BIGGART, J. H. (1936) *Edinb. med. J.*, **43**, 417.
BILLENSTIEN, D. C., and LEVEQUE, T. F. (1955) *Endocrinology*, **56**, 704.
BLOTNER, H. (1937) *New Engl. J. Med.*, **217**, 529.
—— (1950) In: Oxford Loose Leaf Medicine. Edited by H. A. Christian. New York; pp. 1–156.
BODIAN, D. (1951) *Bull. Johns Hopk. Hosp.*, **89**, 354.
——, and MAREN, T. H. (1951) *J. comp. Neurol.*, **94**, 485.
BUCY, P. C. (1930) *J. comp. Neurol.*, **50**, 505.
CROLL, M. M. (1930) *Brain*, **53**, 47.
DIEPEN, R., ENGELHARDT, F., and SMITH-AGREDA, V. (1954) *Anat. Anz.*, **101**, 276.
DINGMAN, J. F., BENIRSCHKE, K., and THORN, G. W. (1957) *Amer. J. Med.*, **23**, 226.
DRAGER, G. A., and RUSSELL, G. V. (1954) *Anat. Rec.*, **118**, 295.
ERÄNKÖ, O. (1951) *Acta physiol. scand.*, **24**, 1.
FORSSMANN, H. (1945) *Acta med. scand.*, suppl. **159**, 1.
GAUPP, R., Jr. (1941) *Z. ges. Neurol. Psychiat.*, **171**, 515.
—— (1944) *Z. ges. Neurol. Psychiat.*, **177**, 50.
GEILING, E. M. K., and OLDHAM, F. K. (1937) *Trans. Ass. Amer. Phycns*, **52**, 132.
GOMORI, G., and CHESSICK, R. D. (1953) *J. Neuropath.*, **12**, 387.
GREEN, J. D., and VAN BREEMEN, V. L. (1955) *Amer. J. Anat.*, **97**, 177.
HENZI, H. (1952) *Mschr. Psychiat. Neurol.*, **123**, 292.
HILD, W. (1954) *Z. Zellforsch.*, **40**, 257.
——, and ZETLER, G. (1951) *Arch. exp. Path. Pharmak.*, **213**, 139.
——, —— (1953) *Pflüg. Arch. ges. Physiol.*, **257**, 169.
JEWELL, P. A., and VERNEY, E. B. (1957) *Phil. Trans.* B., **240**, 196.
KARY, C. (1924) *Virchows Arch.*, **252**, 263.
KIRMAN, B. M., BLACK, J. A., WILKINSON, R. H., and EVANS, P. R. (1956) *Arch. Dis. Childh.*, **31**, 59.
MOGILNITZKY, B. N. (1928) *Virchows Arch.*, **267**, 263.
ORTHNER, H. (1955) In: Handbuch der speziellen pathologischen Anatomie und Histologie. Edited by F. Henke and O. Lubarsch. Berlin; **13**, part 5, p. 543.
PALAY, S. L. (1955) *Anat. Rec.*, **121**, 348.
—— (1957) *Progr. Neurol. Psychiat.*, **2**, 31.
PEPLER, W. J., and PEARSE, A. G. E. (1957) *J. Neurochem.*, **1**, 193.
PORTER, R. J., and MILLER, R. A. (1948) *J. Neurol. Psychiat.*, **11**, 258.
RODECK, H. (1955) *Ergebn. inn. Med. Kinderheilk.*, **6**, 185.
ROMEIS, B. (1940) In: Handbuch der mikroskopischen Anatomie des Menschen. Edited by W. von Moellendorff. Berlin; **6**, part 3, p. 389.
ROTHBALLER, A. B., and DUGGER, G. S. (1955) *Neurology*, **5**, 160.
SCHARRER, E., and SCHARRER, B. (1940) *Res. Publ. Ass. nerv. ment. Dis.*, **20**, 170.
SCHIEBLER, T. H. (1951) *Acta anat.*, **13**, 233.
—— (1952) *Z. Zellforsch.*, **36**, 563.
SLOPER, J. C. (1954) *J. Anat., Lond.*, **88**, 576.
—— (1955) *J. Anat., Lond.*, **89**, 301.
——, and ADAMS, C. W. M. (1956) *J. Path. Bact.*, **72**, 587.
STAEMMLER, M. (1932) *Ergebn. allg. Path. path. Anat.*, **26**, 59.
STUTINSKY, F. (1951) *C. R. Soc. Biol., Paris*, **145**, 367.
TELLO, F. (1912) *Trab. Lab. Invest. biol. Univ. Madr.*, **10**, 143.
TRENDELENBURG, P. (1928) *Klin. Wschr.*, **7**, 1679.
VAZQUEZ-LOPEZ, E. (1942) *J. Anat., Lond.*, **76**, 178.
WEAVER, T. A., Jr., and BUCY, P. C. (1940) *Endocrinology*, **27**, 227.
WICKSEL, M., and CAIN, H. (1952) *Dtsch. Arch. klin. Med.*, **199**, 600.
WINGSTRAND, K. G. (1953) *Z. Zellforsch.*, **38**, 30.

## The Application of Histochemical Methods for Protein Identification in the Study of Certain Pathological Problems

By C. W. M. ADAMS, M.B., B.Ch.
*London*

THE histochemical methods of identifying proteins fall into two classes. The first group comprises those methods which depend on the characteristics of a protein as a whole, such as solubility tests, determination of iso-electric point, reactions and stains for free amino groups and localization by labelled antibodies. The other type of method relies upon the recognition of individual amino acids in protein by specific colour-reactions. It is with these colour-reactions and their application to pathology that this paper is concerned.

These specific reactions depend upon some individual chemical feature of the amino acid concerned, such as the disulphide group of cystine or the 3-indole configuration of trypto-

phane. For this reason it is unlikely that any histochemical colour-tests will ever be devised for the simpler amino acids, such as glycine and alanine, which do not have such characteristic chemical features.

At present the amino acids which can be demonstrated by reliable histochemical methods are: cysteine, cystine, tryptophane, tyrosine and arginine. The chemical reactions involved in some of these methods are still unknown even though, in practice, these methods are quite specific. In this category are the Millon method for the phenolic group of tyrosine and the Sakaguchi method for the guanidinyl group of arginine.

In contrast to these older arbitrary methods, Danielli (1947) has introduced a method for the simultaneous demonstration of tyrosine, tryptophane and histidine. This method relies on exact biochemical principles, namely the combination of these amino acids, in an alkaline medium, with one pole of a tetrazonium compound. In a second stage the diazo group at the opposite pole is coupled with a chromogenic substance to provide sufficient colour for microscopy. The colour developed is, in fact, strong and well defined and this is a most useful method for the general recognition of protein. It has been claimed by Landing and Hall (1956) that a sixth amino acid, histidine, may be stained by a modification of this tetrazonium technique. These authors stated that, after iodine blockade, the staining of the reactive groups of tyrosine and tryptophane was suppressed leaving only histidine to react.

In contrast to the use of diazonium compounds as coupling agents for protein, Lillie (1957) has introduced a method for the direct diazotization of tissue proteins. This application of Morel and Sisley's protein diazotization method is claimed to be a histochemical test for tyrosine. However, the method may not be very specific, for there is evidence (Fraenkel-Conrat, 1951) that tryptophane may also undergo diazotization or nitrosylation with nitrous acid and then combine with aromatic amines and phenols in the same way as diazotized tyrosine (Eagle, 1936).

Cystine and cysteine can be stained by methods which also lend themselves to critical evaluation. The methods for cystine in current use may be classified as either reduction or oxidation techniques. With the reduction methods cystine is converted wholly or in part to cysteine by suitable reducing agents (Barrnett and Seligman, 1954) or by alkaline hydrolysis (Pearse, 1953). In a second stage, the sulphydryl group of the newly-formed cysteine reduces a suitable redox-indicator or sulphydryl-reagent to a coloured product. Certain mercurial compounds and organic halogens can be used to blockade the sulphydryl group and thus confirm the specificity of the test.

The oxidation methods for cystine depend upon the initial oxidation of the disulphide group of cystine to sulphonate. This sulphonate group, which is a highly-ionized acid-radicle, may be linked to certain basic dyes. Now, if the dye is dissolved in strong acid (pH 0·2), the dissociation of all other "tissue" acid-radicles is suppressed, except sulphate and the sulphonate radicle of oxidized cystine. In practice sulphate can be excluded by treating an unoxidized section with the dye alone. It follows that staining seen only in the oxidized section is due to cystine (or cysteine).

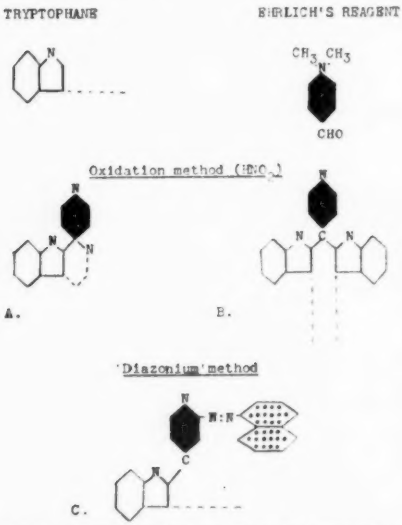



FIG. 1.—Histochemical reactions for tryptophane.

Recently several new histochemical methods have been described for the detection of tryptophane and related indoles. The methods which give the strongest results and which also are the easiest to use depend upon the reaction of tryptophane with Ehrlich's reagent, p-dimethylaminobenzaldehyde. In the simplest of these tryptophane is first condensed with the reagent, after which the resulting compound is oxidized by nitrous acid to a deep blue pigment (Adams, 1957; Glenner, 1957).

It is possible that the blue pigment is a derivative of β-carboline (Fig. 1A) but Glenner has advanced an alternative view that the pigment is Emil Fischer's rosindole compound (Fig. 1B). It is improbable, however, that rosindole is formed since the molecules of tryptophane in a protein would seldom be sufficiently close together to enable two of them, simultaneously, to combine with a molecule of Ehrlich's reagent. Moreover it has been shown

(Giral and Laguna, 1950; Portner and Högl, 1953) that these blue pigments are not formed from indole, the parent substance of tryptophane. This would be difficult to explain by the "rosindole hypothesis", where the side-chain in the "3" position takes no part in the reaction. On the other hand, to form a carboline the side-chain at the "3" position would be essential in order to complete the third ring: carbolines are not formed when the side-chain is either absent or at the "2" position. However, against the "carboline hypothesis", it must be stated that blue pigments are formed *in vitro* from those 3-indolyl derivatives which have insufficient carbon atoms in their side-chain to complete a third ring.

In contrast to these oxidation methods, Glenner and Lillie (1957) have introduced another method for tryptophane, that of coupling a diazonium compound with the indole-Ehrlich compound (Fig. 1c). It is claimed that this reaction takes place at the ortho-position of Ehrlich's reagent although these authors did not exclude coupling with the indole nucleus at the "1" position (Bruemmer *et al.*, 1957).

### Application to Pathological and Experimental Material

These histochemical methods for amino acids may be used to identify the anatomical site of specific proteins known, by biochemical analysis, to be rich in a particular amino acid. Further, the protein in question may then be studied in a semi-quantitative way in both pathological and experimental conditions. To illustrate the application of these methods I propose to refer briefly to some proteins, polypeptides or derivatives of amino acids, where there are unusually high proportions of either cystine or tryptophane (*see* Table I).

Table I.—Amino Acids in Proteins or Tissues (Compiled from various sources)

| Protein or tissue | Approximate content of Cystine % | Tryptophane % | Tyrosine % |
|---|---|---|---|
| Posterior pituitary hormones | 18–19 | 0 | 13 |
| carrier | 17–18 | 0 | 3·4 |
| Li-Sayers protein | 8 | ? | ? |
| Melanophore-stimulating hormone | 0 | 10 | 9 |
| Serotonin | — | equiv. to 100 | — |
| Neurokeratin | 4·3 | 1·8 | 4·9 |
| Pepsin | 1·5 | 2·3 | 10·5 |
| Trypsin | ? | 4·6 | ? |
| Trypsinogen | ? | 2·9 | ? |
| Chymotrypsinogen | 4·5 | 5·4 | 2·9 |
| Liver proteins | 1·4 | 1·6 | 4·1 |
| Muscle proteins | 1·1 | 1·2 | 3·1 |
| Epidermis | 3·0 | 1·8 | 13·9 |
| Hair keratin | 15·9 | 1·3 | 3·0 |
| Whole animal (rat) | 1·9 | 0·7 | 3·2 |

### Neurosecretory Material

The neurosecretory material of the neurohypophyseal system is stained strongly by an oxidation method for cystine (Adams and Sloper, 1956) and in some species by reduction methods as well (Barrnett, 1954; Sloper, 1954, 1955; Howe and Pearse, 1956). This observation is not unexpected since the posterior pituitary hormones and their carrier-protein contain more cystine than any other protein or peptide as yet isolated. Accordingly, it is reasonable to infer that the stainable material contains the active hormones or the carrier or, possibly, both. However, it is likely that the histochemical and staining properties of neurosecretory material are due to the carrier. This may be deduced from the negative reaction of the material for tyrosine, a finding which is more consistent with the small fraction of tyrosine in the carrier than with the high proportion of this amino acid in the active hormones (*see* Table I).

### Crooke-Russell Cell

Certain pituitary basophils, including the Crooke-Russell cell, contain muco-protein granules rich in cystine. The granules of these cells were stained blue by an oxidation method for cystine (performic acid-alcian blue) while the granules of the other basophil, containing little cystine, were stained red by PAS (Adams and Swettenham, 1958). This method is a development of the performic acid-aldehyde-fuchsin technique used by Russell (1956) for distinguishing beta and delta basophils in the human pituitary.

There is only one protein or hormone, as yet isolated from the adenohypophysis, which contains such a characteristic amount of cystine: this is the protein which was isolated by Li, Evans and Simpson and by Sayers *et al.* in 1943 (*see* Table I). This Li-Sayers protein was thought at first to be ACTH, but this claim was later shown to be wrong (Astwood, *et al.*, 1952). Meanwhile, Sayers (1952) has suggested that the protein may be a carrier for ACTH. Our observations on the basophils in Addison's disease at least support the opinion that the protein is related to the formation of ACTH.

### Melanophore-stimulating Hormone

Extracts of the pars intermedia of lower mammals and vertebrates have an expanding action on the melanophores of the frog dermis. The hormone responsible for this effect is now known to be a polypeptide containing about 10% of tryptophane (Harris and Ross, 1956). When the corresponding histochemical test for tryptophane was applied to the frog pituitary fine blue granules were seen in the basophils of the pars intermedia. It has not yet been possible, however, to determine by experimental means whether these granules are, in fact, the active melanophore-expanding hormone.

### Serotonin (5-Hydroxytryptamine)

Since serotonin is a derivative of tryptophane, a strong reaction with the carboline method might be expected in the argentaffin granules of the alimentary tract and carcinoid tumours. In practice argentaffin granules could not be identified by this method. The failure here was possibly a result of formalin fixation, for formaldehyde could prevent the reaction by combining with serotonin in the same way as does Ehrlich's reagent. The difficulty arises, as reported by Barter and Pearse (1953), that the granules cannot be seen unless formalin fixation is used. However, in an alcohol-fixed carcinoid tumour a fairly strong reaction was found in the peripheral cells of the trabeculæ, the site of the argentaffin granules in the formalin-fixed blocks of the same tumour. Nevertheless, as with the melanophore-stimulating hormone, it does not follow that the stained material was the active hormone, for any of the precursors of serotonin, such as 5-hydroxytryptophane or even tryptophane, could also have given a positive reaction.

### Neurokeratin

In contrast to the secretory proteins the next example is a structural protein of the nervous system. Neurokeratin was first isolated as a soda-insoluble substance from the brain by Ewald and Kühne (1877), but little was known about the nature of "neurokeratin" proteins until the recent work of Folch and Lees (1951) and LeBaron and Folch (1956). Some distinguishing features of these proteins are that they are resistant to digestion by trypsin, pepsin and papain and that they contain about 1·8% of tryptophane. These features lend themselves to the anatomical localization of the neurokeratins, for when sections of alcohol-fixed brain and peripheral nerve were digested in trypsin and stained for tryptophane only the myelin sheath was still seen. The proteins of the ground substance and glial fibres had disappeared while a considerable part of the myelin protein was undigested. This suggests that the neurokeratins are derived from the myelin sheath, probably from the protein layers which have been described in myelin lamellæ by Fernández-Morán (1950) and Finean (1953).

During Wallerian degeneration of the peripheral nerve, at the early stage before the lipids are chemically degraded (Johnson *et al.*, 1950), the myelin lipids appeared to be dissociated physically from the neurokeratin or protein material. It is likely, therefore, that this dissociation of lipid from protein is an important factor in demyelination since it occurs before the stage of chemical degradation of myelin. We have not yet established, however, whether this type of dissociation also occurs during demyelination in the C.N.S.

### Experimental Protein Malnutrition

As part of an investigation on protein malnutrition in experimental animals (Adams *et al.*, 1958) a low protein/high carbohydrate diet (cassava) was fed to rats and mice and a study was made of the effect of this deficiency on the proteins of zymogen, liver and muscle. The intense reaction for tryptophane found in pancreatic, submandibular ("serous tubular"), peptic and Paneth cell zymogen of normal animals was probably due to the presence of tryptophane-rich proteolytic enzymes (*see* Table I). The number of zymogen granules in these secretory cells decreased quite early in the course of protein malnutrition. This was associated in the pancreas with atrophy of acini and in the submandibular gland with marked shrinkage of the zymogenic "serous tubules". At the same time there was considerable loss of cytoplasmic protein from the liver but no comparable loss of protein from muscle (tryptophane) or from the epidermis (cystine, tyrosine and arginine).

Davies (1948, 1952) has suggested that the pancreatic changes are the essential feature of kwashiorkor, a disease of tropical children nourished on low protein/high carbohydrate diets. He regarded the atrophy and degranulation of pancreatic acini as more fundamental than the fatty change in the liver.

However, in our experimental animals, fed on a diet of cassava, both the pancreas and the liver were affected simultaneously as regards loss of protein. Furthermore, the protein-loss from the liver bore no relationship to the degree of fatty change found. It is likely, if the experimental animal can be compared with the human, that the same may apply in kwashiorkor. Sprinson and Rittenberg (1949) have found that the turnover of labelled protein in the liver is about 3½ to 15 times as rapid, depending upon the species, as that of protein in

muscle and skin. This may account for the considerable loss of protein from liver when compared with our failure to detect a loss from skin and muscle.

Clearly there is much scope for the use of histochemical protein methods in experimental pathology.

## REFERENCES


ADAMS, C. W. M. (1957) *J. clin. Path.*, **10**, 56.
——, FERNAND, V. S. V., and SCHNIEDEN, H. (1958) *Brit. J. exp. Path.* (in press).
——, and SLOPER, J. C. (1956) *J. Endocrinol.*, **13**, 221.
——, and SWETTENHAM, K. V. (1958) *J. Path. Bact.*, **75**, 95.
ASTWOOD, E. B., RABEN, M. S., and PAYNE, R. W. (1952) *Recent. Progr. Hormone Res.*, **7**, 1.
BARRNETT, R. J. (1954) *Endocrinology*, **55**, 484.
—— and SELIGMAN, A. M. (1954) *J. Nat. Cancer Inst.*, **14**, 769.
BARTER, R., and PEARSE, A. G. E. (1953) *Nature, Lond.*, **172**, 810.
BRUEMMER, N. C., CARVER, M. J., and THOMAS, L. E. (1957) *J. Histochem. Cytochem.*, **5**, 140.
DANIELLI, J. F. (1947) *Symp. Soc. exp. Biol.*, **1**, 101.
DAVIES, J. N. P. (1948) *Lancet*, i, 317.
—— (1952) *Annu. Rev. Med.*, **3**, 99.
EAGLE, H. (1936) *Proc. Soc. exp. Biol., N.Y.*, **34**, 39.
EWALD, A., and KÜHNE, W. (1877) *Verhandl. Naturhist-Med.*, **1**, 457. Cited by LeBaron and Folch (1956).
FERNÁNDEZ-MORÁN, H. (1950) *Exp. Cell Res.*, **1**, 309.
FINEAN, J. B. (1953) *Exp. Cell Res.*, **5**, 202.
FOLCH, J., and LEES, M. (1951) *J. biol. Chem.*, **191**, 807.
FRAENKEL-CONRAT, H. (1951) In: Amino Acids and Proteins. Editor D. M. Greenberg. Springfield, Ill., p. 560.
GIRAL, J., and LAGUNA, J. (1950) *Ciencia, Méx.*, **10**, 83.
GLENNER, G. C. (1957) *J. Histochem. Cytochem.*, **5**, 297.
——, and LILLIE, R. D. (1957) *J. Histochem. Cytochem.*, **5**, 279.
HARRIS, J. I., and ROOS, P. (1956) *Nature, Lond.*, **178**, 90.
HOWE, A., and PEARSE, A. G. E. (1956) *J. Histochem. Cytochem.*, **4**, 561.
JOHNSON, A. C., MCNABB, A. R., and ROSSITER, R. J. (1950) *Arch. Neurol. Psychiat., Chicago*, **64**, 105.
LANDING, B. H., and HALL, H. F. (1956) *Stain Tech.*, **31**, 197.
LEBARON, F. N., and FOLCH, J. (1956) *J. Neurochem.*, **1**, 101.
LI, C. H., EVANS, H. M., and SIMPSON, M. E. (1943) *J. biol. Chem.*, **149**, 413.
LILLIE, R. D. (1957) *J. Histochem. Cytochem.*, **5**, 528.
PEARSE, A. G. E. (1953) *J. Histochem. Cytochem.*, **1**, 460.
PORTNER, C., and HÖGL, O. (1953) *Analyt. Chim. Acta*, **8**, 29.
RUSSELL, D. S. (1956) *Proc. R. Soc. Med.*, **49**, 1018.
SAYERS, G. (1952) *Rec. Progr. Hormone Res.*, **7**, 51.
——, WHITE, A., and LONG, C. N. H. (1943) *J. biol. Chem.*, **149**, 425.
SLOPER, J. C. (1954) *J. Anat., Lond.*, **88**, 576.
—— (1955) *J. Anat., Lond.*, **89**, 301.
SPRINSON, D. B., and RITTENBERG, D. (1949) *J. biol. Chem.*, **180**, 715.


# Some Histochemical Aspects of Pædiatric Pathology, with Remarks on Quantitation in Histochemistry


By IRVINE J. HUNTER, M.B., B.Sc.

*Research Fellow in Histochemistry, The Hospital for Sick Children, London*


HISTOCHEMICAL techniques such as micro-incineration, X-ray diffraction and autoradiography are specialised tools of research, and rather far removed from classical morbid anatomy, as, for that matter, is the morphological world of the electron microscopist. On the other hand, that part of the general field of histochemistry which may be designated "histochemical staining" can be regarded as an extension and expansion of classical morbid anatomy by other or more refined techniques. Indeed, some histochemical techniques, such as the periodic-acid-Schiff method (Hotchkiss, 1948; McManus, 1946, 1948*a*, *b*), have been incorporated into the normal armamentarium of morphological diagnosis. (Originally suggested as a histological method it was later accepted as a histochemical method (*see* Pearse, 1953), and has been received into histology in its histochemical setting.)

I wish briefly to consider the interrelation of histochemical staining and allied procedures with morphological histopathology, using a few diseases of childhood merely as examples, and to conclude with some remarks on the question of quantitation in the field of histochemical staining.

Histochemical techniques may be used as an adjunct to histopathological diagnosis, as in the demonstration of motor end-plates of muscle by their acetyl-cholinesterase activity (see Woolf and Till, 1955). In a few instances the diagnosis may fall largely on the histochemist, for example in the condition of hypophosphatasia, first described by Rathbun

(1948), which clinically has some resemblance to rickets. In this condition impaired osteogenesis, apparently primary (Fraser *et al.*, 1955), often leading to craniostenosis, is associated with deficient alkaline phosphatase in the bones (*see* Schlesinger *et al.*, 1955; Fraser, 1957). Since in some cases the blood alkaline phosphatase may be within normal limits, the definitive diagnosis may depend on chemical and histochemical demonstration of grossly lowered alkaline phosphatase activity in a bone biopsy. An article in "Recent Advances in Clinical Pathology" gives details of the applicability of histochemical methods to general diagnostic histology. This was written by the late George Gomori, whose sudden and untimely death earlier this year was indeed a bitter blow to the science of histochemistry.[1]

Turning to the application of histochemistry in the investigation of problems of disease—the histochemist usually begins with a problem which appears incapable of solution by the means at the disposal of classical morbid anatomy. After the chemical phase of the procedure is over there comes the histological. Under the microscope, the result must be analysed from both the chemical and morphological points of view, so that a sound knowledge of morphology is essential for the interpretation of the results of histochemical (and, one might venture to add, of experimental) research in pathology.

Dr. C. W. M. Adams has illustrated ways of staining proteins by means of the demonstration of specific groups in particular amino acids, the best known of these methods being the classical reaction of Millon (1849), modified by subsequent workers such as Bensley and Gersh (1933), which demonstrates the phenolic group of tyrosine. I should like to illustrate the other major type of reaction used histochemically to demonstrate protein, namely staining with acidic dyes in acid solution. Every histologist knows that "eosinophil" is an equivalent of "acidophil"; these methods are thus fundamentally the familiar eosin-staining of the cytoplasm in a different guise, using more precise stains under more controlled conditions. The principles of staining by acid and basic dyes were considered by Singer (1952).

The acidophilic properties of proteins depend in practice upon three chemical groupings—the guanidinyl group of arginine, the epsilon-amino group of lysine, and the imidazyl group of histidine.[2] At acid pH, the coloured anion of acid dyes will combine with these basic groups and stain the protein. In comparison with the methods which demonstrate specifically groupings in particular amino acids these methods are not, to the same extent, chemically specific for proteins, but are convenient for their demonstration, especially for the histone of the nucleus, which, because it is more basic than the cytoplasmic proteins, can be differentially stained by using a solution with a lesser concentration of hydrogen ions. The principle is similar to the use of solutions of greater hydrogen-ion concentration for differential staining by basic dyes, of basophilic substances, a procedure made use of in the well-known methylene-blue extinction test introduced by Pischinger (1926, 1927*a*, *b*), and used particularly by Dempsey and Singer (1946), and their co-workers (Dempsey *et al.*, 1947; Singer and Morison, 1948; Dempsey *et al.*, 1950).

The staining of protein by naphthol yellow S in acid solution was described by Deitch (1955). Similar results can be obtained with the better-known chemically related stain, Martius yellow.[3] In a section of tongue it is apparent that everything is stained a deep yellow except the mucus-secretion in the glandular cells. (The author showed a number of photomicrographs taken from children with fibrocystic disease of the pancreas.)

At this point we may make a diversion to consider a histochemical trichrome staining method described by Himes and Moriber (1956). Azure A is one of the stains which are formed as a result of the polychroming of methylene-blue (*see* Conn, 1953). The work of Kramer and Windrum (1955) has shown that azure A is to be preferred to thionine, and is more rational than toluidine blue, for the demonstration of metachromasia of mucin. It has, however, other uses: it can be used as a basic dye, to stain nucleic acids in general (being so used by Pollister, 1950); and after Feulgen hydrolysis of the section with hydrochloric acid it acts, in acid metabisulphite solution, as a specific nuclear stain. This leaves leucofuchsin for use in the periodic-acid-Schiff reaction, and finally protein can be stained with naphthol yellow S. The yellow goes into the nuclei, converting the blue of the azure A to green. The result with this method differs from the histological trichrome methods, such as iron hæmatoxylin, van Gieson and Masson's stain, in that collagen and muscle are not differentially stained. Its purpose is, of course, quite different—to show, not general structure, but distribution of chemical substances.

[1]Born in 1904 at Budapest; died on February 28, 1957. In the original Hungarian his name was Gömöri, pronounced "Gúmmery", but the anglicized version is established by usage, and, in this instance, is justified by the fact that his adopted country was the United States of America. A short account of his career (Lillie, 1957) was published in *The Journal of Histochemistry and Cytochemistry*.

[2]Almost all alpha-amino groups in proteins are, of course, occupied in peptide linkages, but a small fraction of the basic properties may be due to the few terminal alpha-amino groups.

[3]Naphthol yellow S is the dipotassium salt of flavianic acid. Martius yellow (sometimes known as naphthol yellow) is the salt of an acid which lacks the sulphonic acid group present in flavianic acid.

Another dye that may be used for the staining of proteins is fast green F.C.F., which is of interest as the dye which first focused attention on the anionic staining of proteins as a histochemical procedure, when it was utilized for this purpose by Schrader and Leuchtenberger (1950).[1] A section of ileal mucosa from a case of meconium ileus, stained by fast green at a very acid pH (about 1·5), shows that everything, including the glandular mucin, is stained green at this pH, the red blood corpuscles and the more condensed material of the intestinal contents staining in a much deeper shade. When hyaline cartilage is stained with basic dyes and basic dye lakes the nucleic acid of the nucleus and the acid mucopolysaccharide of the matrix are stained, whereas here a similar histological effect is obtained by staining the protein in these two structures.

So far we have been considering the demonstration of features which may not be apparent by classical morphological staining. However, on occasions histochemical methods may be used to demonstrate as well as, if not better than, the usual impregnation or staining methods, the structural niceties of classical morphology. Fig. 1 is tongue muscle, stained by fast green, showing quite clearly not only the Q band (light) and J band (dark), but also the Z line (light) in the J band and the M line (dark) in the Q band. The result is thus the opposite of that obtained with basic dyes and dye lakes, such as iron hæmatoxylin, and similar to that seen with silver impregnation and polarized light, the isotropic segments being stained more deeply. The staining of the cross striations of muscle by acid and basic dyes was investigated by Dempsey *et al.* (1946), using orange G as their acid dye.

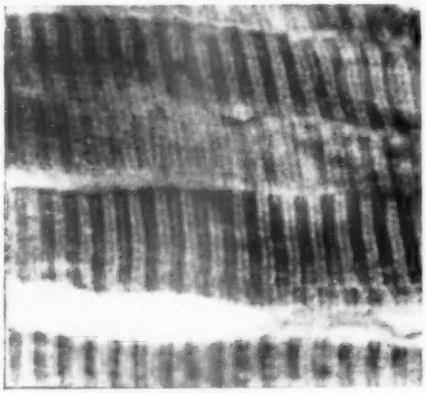


FIG. 1.—Tongue muscle from a child aged 9 months, showing the cross striations. ×2,000. Stained by fast green F.C.F. at approximately pH 3·0, M/5 acetate buffer. The isotropic segments are deeply stained.

Thirdly, the use of histochemical methods may bring to light morphological problems which were not apparent before. Consider the obstructed segment in a case of meconium ileus, a condition thought to be, at least in the great majority of instances, a manifestation in the neonatal period of fibrocystic disease of the pancreas (*see* Bodian, 1952). In a preparation stained by hæmatoxylin and eosin, the intestinal contents, while not homogeneous, appear amorphous, and hardly inspire one to attempt a morphological analysis. When stained by the trichrome method mentioned above, using Feulgen hydrolysis and azure A, periodic-acid-Schiff, and naphthol yellow S, the impression is entirely different. The discrete distribution of protein and mucopolysaccharide staining, the areas of protein being associated with numerous nuclei, and the presence of rounded, more compact areas, suggest the possibility that there is here a morphological problem to be solved, and lead one to doubt the current view that the blockage is to be adequately explained merely by the inspissation of more than usually viscous mucoid material.

Thus, histochemical methods, apart from assisting in diagnosis, may be used to investigate the problems of disease, to demonstrate morphological structure, and may themselves uncover morphological problems which were not apparent before.

*Quantitation of Histochemical Staining*

There is a growing tendency to measure the colours obtained by histochemical staining by use of the microspectrophotometer.

A number of people, notable among whom are Caspersson (1947) and Danielli (1953), have set out in detail the optical requirements for accurate quantitation by this method. A second essential is that the intensity of colour should bear a quantitative relationship to concentration of the chemical substance demonstrated (*see* Allfrey *et al.*, 1952). It is obvious that some investigators have made no attempt to fulfil the requirements under these headings. However, such difficulties may be overcome by ingenuity, patience and attention to detail.

A third and more important type of difficulty in achieving quantitation in histochemistry is

[1] Introduced first as a food dye by Johnson and Staub (1927), and as a histological stain by Haynes (1933), it was adopted by Lillie (1940) for use in place of light green in Masson's trichrome stain.

inherent in the tissue with which we work, and is posed by the non-uniform distribution of chemical substances in biological tissues and cells. This problem was succinctly and graphically dealt with by Gomori (1952) in his book "Microscopic Histochemistry". Suppose we have a given amount of coloured substance continuously and uniformly distributed which allows transmission of 5% of light of the wavelength used—in other words a dark colour. If the same amount of coloured substance is discontinuously distributed so that it covers only half the field, the amount transmitted will be 52·5%, and if aggregated to cover a tenth of the field, 90·5% of the light will be transmitted. The range of error is thus enormous. If the colour is lighter, the error is less, but still substantial. If the transmission with uniform distribution is 50%, the other figures will be 75% and 95%.

I do not wish to detract in the least from the achievement of some workers, such as Caspersson and his school, in applying quantitative methods to histochemistry, although one feels that at times their claims are somewhat optimistic. I do wish, however, to suggest that all claims of quantitation in the field of histochemical staining should be received in a spirit of scepticism and subjected to the closest scrutiny before being accepted. Certainly one should strive to replace, where possible, subjective assessment by objective measurement, but the judgment of a trained observer is still to be preferred to the spurious accuracy of misleading figures. Whether accuracy of quantitation has, in fact, been achieved can perhaps only be judged by the expert with knowledge of the optical system used and the chemical reaction involved; but it is the knowledgeable morphologist who is in the best position to decide whether or not, in any given circumstances, quantitative methods may be validly used.

I have mentioned the extrinsic and intrinsic technical difficulties of quantitation as applied to histochemical staining, leaving aside the wider questions of possible differences in the localization and amount of chemical substances in dead as compared with living tissues, and of artefactual effects produced during treatment of the tissues.

Certainly, accurate quantitation is occasionally possible in histochemistry, and somewhat more commonly a very rough degree of quantitation is possible and may give significant results, but, it is suggested, with almost all problems the only quantitation which has validity and significance is of the order—yellow, very yellow, faintly yellow, or not yellow at all.

## REFERENCES


ALLFREY, V., STERN, H., MIRSKY, A. E., and SAETREN, H. (1952) *J. gen. Physiol.*, **35,** 529 (addendum).
BENSLEY, R. R., and GERSH, I. (1933) *Anat. Rec.*, **57,** 217.
BODIAN, M., Ed. (1952) Fibrocystic Disease of the Pancreas. London.
CASPERSSON, T. (1947) *Symp. Soc. exp. Biol.*, **1,** 127.
CONN, H. J. (1953) Biological Stains. 6th. Edn. Geneva, New York; p. 109.
DANIELLI, J. F. (1953) Cytochemistry. New York; p. 126.
DEITCH, A. D. (1955) *Lab. Invest.*, **4,** 324.
DEMPSEY, E. W., BUNTING, H., SINGER, M., and WISLOCKI, G. B. (1947) *Anat. Rec.*, **98,** 417.
——, and SINGER, M. (1946) *Endocrinology*, **38,** 270.
——, SINGER, M., and WISLOCKI, G. B. (1950) *Stain Tech.*, **25,** 73.
——, WISLOCKI, G. B., and SINGER, M. (1946) *Anat. Rec.*, **96,** 221.
FRASER, D. (1957) *Amer. J. Med.*, **22,** 730.
——, YENDT, E. R., and CHRISTIE, F. H. E. (1955) *Lancet*, i, 286.
GOMORI, G. (1951) In: Recent Advances in Clinical Pathology. Ed. S. C. Dyke. 2nd Edn. London; p. 472.
—— (1952) Microscopic Histochemistry. Chicago; p. 20.
HAYNES, R. (1928) *Stain Tech.*, **3,** 40.
HIMES, M., and MORIBER, L. (1956) *Stain Tech.*, **31,** 67.
HOTCHKISS, R. D. (1948) *Arch. Biochem.*, **16,** 131.
JOHNSON, H., and STAUB, P. (1927) *Industr. Engng Chem. (Industr.)*, **19,** 497.
KRAMER, H., and WINDRUM, G. M. (1955) *J. Histochem. Cytochem.*, **3,** 227.
LILLIE, R. D. (1940) *Stain Tech.*, **15,** 17.
—— (1957) *J. Histochem. Cytochem.*, **5,** 203.
MCMANUS, J. F. A. (1946) *Nature, Lond.*, **158,** 202.
—— (1948*a*) *Amer. J. Path.*, **24,** 643.
—— (1948*b*) *Stain Tech.*, **23,** 99.
MILLON, E. (1849) *C. R. Acad. Sci., Paris*, **28,** 40.
PEARSE, A. G. E. (1953) Histochemistry. London; p. 135.
PISCHINGER, A. (1926) *Z. Zellforsch.*, **3,** 169.
—— (1927*a*) *Z. Zellforsch.*, **5,** 347.
—— (1927*b*) *Pflüg. Arch. ges. Physiol.*, **217,** 205.
POLLISTER, A. W. (1950) *Rev. Hémat.*, **5,** 527.
RATHBUN, J. C. (1948) *Amer. J. Dis. Child.*, **75,** 822.
SCHLESINGER, B., LUDER, J., and BODIAN, M. (1955) *Arch. Dis. Childh.*, **30,** 265.
SCHRADER, F., and LEUCHTENBERGER, C. (1950) *Exp. Cell Res.*, **1,** 421.
SINGER, M. (1952) *Int. Rev. Cytol.*, **1,** 211.
——, and MORISON, P. R. (1948) *J. biol. Chem.*, **175,** 133.
WOOLF, A. L., and TILL, K. (1955) *Proc. R. Soc. Med.*, **48,** 189.

[*January* 21, 1958]

# The Problem of Cancer of the Lung in the Industrial Area of Liège during Recent Years

By Professor J. FIRKET

*Directeur, Institut de Pathologie, Liège, Belgium*

(With the assistance of the late Professor Batta, and of Mme Castermans, M. Desoignies, M. Van Lancker, Mlle Thomas)

THE information that we acquired from the study of air pollution in Liège is our reason for giving this paper.

At the end of December 1930 a dense, poisonous fog occurred in the Meuse valley. There were about 9,000 people living in an area, half rural, half industrial, who suddenly collapsed on the third or fourth day of this severe fog—80 of whom died a few hours later. The fog had spread all over the east of Belgium. It was not specially dense in Liège, but was very noxious in the industrial valley for a distance of 10 to 15 kilometres directly upstream from Liège. In that area most of the patients, and especially those who died, showed on the third or fourth day slow, gasping breathing, cardiovascular failure, hypotension and alkalosis (Fig. 1). Death occurred after only a few hours.

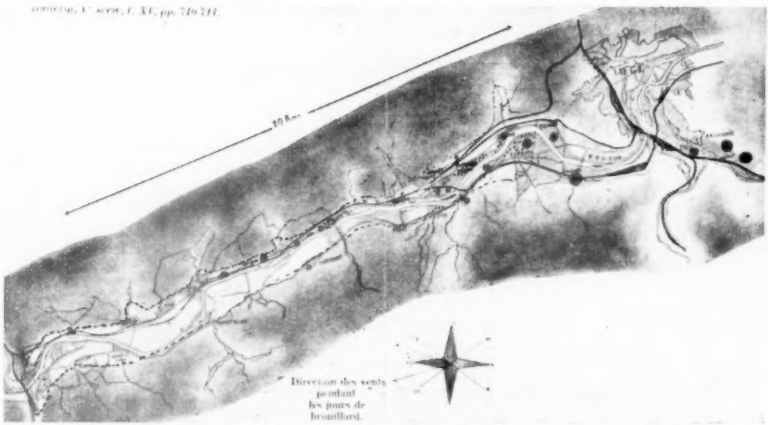


FIG. 1.—Chart of the toxic fogs in the Meuse Valley, upstream from Liège.

*Reproduced from Firket (1931) by kind permission.*

While carrying out our research we found the results of some chemical analyses in the University archives which had been made quite fortuitously during the year 1899. In these the quantity of sulphur on the soil had been measured immediately after snow had fallen and washed the atmosphere while falling. In the same places, thirty years later, our chemists found ten times as much sulphate in equivalent amounts of freshly fallen snow.

During the year 1931 we asked our British colleagues, in particular Dr. J. B. Haldane, how toxic incidents, similar to those we had experienced upstream from Liège, had never been observed in London during dense fogs which lasted longer than ours. Haldane replied that heat emanation from such a large concentration of people living in London, prevented the meteorological ceiling from descending so near to the ground and that therefore the fog polluted by industrial smoke could spread freely and laterally towards the neighbouring hills around the city. In fact, we know that particles of soot, acidified or not by $SO_2$, dissolved in water from the fog, did not fall quickly to a level where human beings could inhale them. The risk of London fogs reaching a threshold of toxicity was not therefore, at that time, so great and severe respiratory complications were less likely to occur. If we use Stokes' formula, we find that, during cold, foggy weather with no wind, a particle of soot 1 $\mu$ in diameter and issuing from a chimney 80 metres high takes six days to reach the ground. Similarly, in the same meteorological conditions, a particle 2 $\mu$ in diameter would take about three days, and a particle measuring 4 $\mu$, one and a half days.

The steady increase of air pollution in industrial communities during the last half-century is well demonstrated by the three following dates: Professor Prost's results of 1899, the experts' analyses in Liège in 1931 and the London experience of 1952.

But how may these dense, smothering fogs be related to the increased incidence of pulmonary cancer observed at the present day?

The meteorological conditions which caused the heavy mortality in 1930 are quite unusual in Liège. They were caused by the following series of events: a considerable cooling of thick dusty air, a fog filled with fumes (especially sulphurous ones), an east wind of only 1 km. per hour and a meteorological ceiling hanging at an average of 75 metres above the ground. The ceiling was thus lower than the tops of the hills bordering the valley, which are mostly about 80 metres high. The wind was blowing *upstream* very nearly in the direction of the valley. It carried along with it all the dust from the town and although fog covered the town no symptoms of poisoning were reported among its inhabitants.

Similar conditions over a period of over four days have been seen only five times from 1901 to 1930. Twice they caused comparable accidents; once they did less harm, by occurring in a branch rather than in the main valley of the Meuse; and on two occasions they happened during a period when industrial activity was much below normal.

Table I shows the substances which were measured more especially, namely those which caused acute symptoms on the third and fourth days of fog.

TABLE I.—MEASUREMENTS ON 20 KM. OF THE VALLEY UPSTREAM FROM LIÈGE AND TOWARDS HUY

| Nature of products | Toxic content after several hours of exposure | Maximum content reached after 1 day | Maximum content reached after 4 days |
|---|---|---|---|
| $CO_2$ | More than 2% by volume | About 0·4% by volume | About 1½% by volume |
| CO | More than ½% | About 0·03% by volume | About 1½% by volume |
| $NO_2$ | 12 to 16 cg. per cubic metre of air | 1 to 2 mg. per cubic metre | 4 to 8 mg. per cubic metre |
| HF | In the region of 4 mg. per cubic metre of air | 0·08 mg. per cubic metre | 0·3 mg. per cubic metre |
| $SO_2$ | 20 to 30 mg. per cubic metre of air | 25 mg. per cubic metre | 100 mg. per cubic metre |
| $H_2SO_4$ | 4 mg. per cubic metre of air | 38 mg. per cubic metre | 152 mg. per cubic metre |
| | | (On supposition of the complete oxidation of $SO_2$.) | |

A similar smog occurred in 1948 in Donora, an industrial valley in Pennsylvania, and, like the Meuse incident of 1930, aroused the interest of the whole world.

We now have to consider whether the same amount of gaseous substances, including not only the polluted air of the valley but also the air of the city, might not, in some other conditions, bring cancer in its train.

We know that the meteorological conditions which provoked such toxic effects upstream from the Meuse were quite unusual as far as the direction of the wind is concerned. Indeed, the prevailing wind is from west-south-west. It is generally not very strong, with an average speed of 5 to 10 km. per hour. In a general way, Liège and its outskirts which include 500,000 inhabitants live in a foggy or a smoky atmosphere, extending over a wider stretch of ground. Hills border the city on the north side and are about as high as those limiting the valley upstream. Those special conditions should be taken into account when we examine the particular geographical factors of the region, even if they do influence conditions for only a very short time.

When we try to explain the increase in frequency of primary cancer of the lung which has been observed these last forty years in Liège, as well as in Western Europe and in America, we cannot find a single determining factor in any given region. Undoubtedly, primary lung cancer has always existed. When I was in my twenties, it was uncommon, just as primary cancer of the liver still is in Europe, though frequent in the tropics. And when it first became obvious, say between 1920 and 1930, we believed the increase in frequency to be only apparent and resulting from better methods of radiological, cytological or clinical detection. It gradually became clear, however, that the increase was real.

For the last fifty-four months we have diagnosed, in the whole Province of Liège, 820 cases of primary pulmonary cancer, of whom 788 were men and 32 women. All these cases were confirmed either by biopsy or through exfoliative cytology or by both. Among the 900,500 citizens in the province a number of pulmonary cancers must have escaped our microscopic investigation. If this disease were spreading throughout Belgium among the population at the same rate, it might be said the total number of patients suffering from pulmonary cancer in the whole country was about 6,000. These figures almost agree with the Dutch cancerologist Korteweg's opinion, when he says that primary lung cancer is

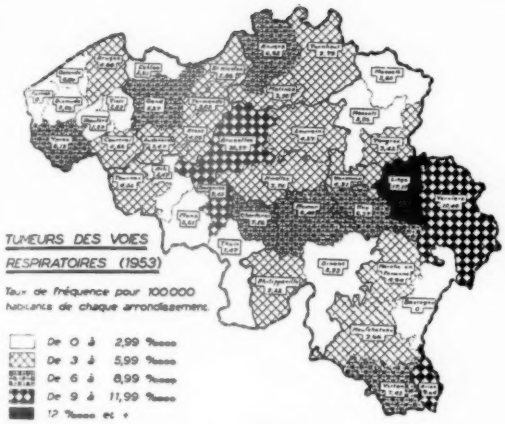



FIG. 2.—Map of Belgium giving the primary lung cancer in the different districts.
*Reproduced from Tuyns (1954) by kind permission.*

fast approaching 40% of the total mortality due to cancer in Western Europe. Those figures should draw the attention of the Belgian medical authorities to the fact that unless 250 or 300 new cases of pulmonary cancer per year are discovered out of every one million of Belgians (a number below the populations of each of the provinces of Antwerp, Brabant, and Flanders and Hainaut) our methods of examination have not been sufficiently thorough (Fig. 2).

In our province of Liège we appear to have the highest incidence in the whole of Belgium. But, until we can be sure of the efficiency of our detection system throughout the country we do not feel justified in concluding that the incidence varies in the different regions. No doubt our province has been somewhat favoured because all pathological and microscopic examinations are centralized in our Department of Pathology. This department is run as a public service and during the last five years has undertaken more exfoliative cytology than any other centre in Belgium.

Why primary cancer of the lung has been increasing is one of the most important problems of pathology which our generation has to face. Some types of lung cancer seem to be particularly responsible for the general increase. Next in frequency were two other types of adenocarcinoma: pulmonary adenomatosis and cancer arising from bronchial glands (Figs. 3, 4, 5).

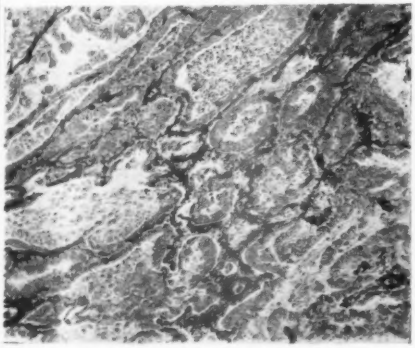


FIG. 3.—Adenomatosis with mucus in the epithelial cells and elastic fibres of the stroma stained.

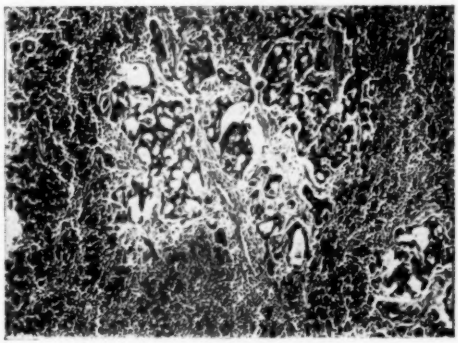


FIG. 4.—Metastasis of the same cancer in a hilar gland.

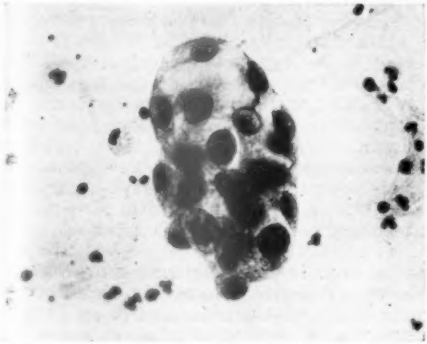


FIG. 5.—Smear by the Papanicolaou method of an adenomatosis.

In 1942, Neubuerger and Geever identified 25 cases definitely similar to these last, and 15 doubtful ones. In 1954 one of my assistants, Dr. Desoignies, reported 4 such cases. The comparatively small number of this type of case, which seems to affect women as well as men and often leads to metastases or to several secondaries, seems to constitute a particular type, "the alveolar tumour". This appears to be as malignant as any other type of pulmonary tumour. Morphologically it has been compared with the "jaakziekte" of sheep which is certainly due to worm infestation (Dungal, 1946). With many others we tend not to classify these last tumours with those we referred to at the beginning. But the question has become all the more important since Campbell and Kreyberg (1956) appear not to agree with this opinion. The fact that tumours of Kreyberg's second group occur in an equal number of men and women seems to point to endocrine origin.

Both by clinical observation of human cancers and by experimental cancerology, certain aspects of the pathogenesis of spontaneous cancers are well established.

Firstly, it seems clear that every cancer requires a previous alteration in the tissues from which it originates. This alteration may be either regenerative, hyperplastic or metaplastic, and precedes the appearance of cancer sometimes by many years. Recent observations of cancers "in situ" help to illustrate this fact. Secondly, any cancer is almost certainly the result of the cumulative or combined action of several factors, intrinsic or extrinsic, of which each particular form of cancer has its own combination. The causes may be the presence of a virus, deficiency of a food, exogenous or endogenous toxin, or the lack or excess of a genetic or endocrine factor. I am convinced that in the present case, carcinogenic hydrocarbons play a part and 3:4 benzpyrene a predominant one. Stocks and Campbell (1955) show figures from England and Wales which indicate that certain quantities of benzpyrene, expected to have been inhaled with air or cigarette smoke play a most important part. This was the basis for further work devoted to pulmonary incidence of various degrees of air pollution, in other countries where conditions are quite different. Thirdly, any spreading cancerization is the result of carcinogenic factors that must exert their action for a very long time. Pulmonary cancers observed in the miners of Schneeberg, which certainly may be ascribed to radioactive dust from nickel, arsenical cobalt, silver, &c., did not appear until at least eighteen years had been spent at work in the dusty galleries. Often they only appeared several years after the men had ceased from this noxious work.

But apart from these general ideas, we are much less well informed as to the part in carcinogenesis played by chronic infectious processes in the bronchi, chronic bronchopneumonia, bronchiectasis, the effects of poison gas, or by psittacosis. We cannot believe that the pandemic influenza towards the end of the First World War bears a particularly heavy responsibility, in spite of the bronchial metaplasia it caused. Moreover, in 1923, Staehelin (1919) in Basel pointed out that his post-mortem department had recorded an increase in the frequency of primary pulmonary cancers which had started in 1912—some five years before the 1917 epidemic of influenza. A similar observation had been made by Mönckeberg in Strasbourg before 1914.

The direct experimental approach to the problem in man seems very promising when we consider that several chemicals may lead to primary tumours in lower animals following their inhalation and especially in view of Blacklock's (1957) evidence that the intrapulmonary inoculation of hydrocarbons such as 3:4 benzpyrene or methylcholanthrene can induce both sarcoma and carcinoma of the lung in rats. Yet, it is certain that though several tumours have been produced, none has resulted from a direct action of a carcinogenic hydrocarbon on the respiratory epithelium. They have certainly been produced in sarcomas in the body of the tissue but not in the recovering epithelium. That is why the experimental techniques used by Andervont (1939) by means of threads set with crystals of dibenzanthracene were able to transform recovering epithelium into one type of cell or another. Thus one is struck by the numerous factors which lead to a similar result. Over 200 organic substances, or even plain metals, proved to be carcinogenic towards one animal species or another, by means of such a technique.

On the other hand, virus, food deficiencies, hormonal alterations, and radio-activity can have a similar effect. And we must only conclude that carcinogenic agents are so many and so diverse that it is virtually impossible for any tissue to escape all exposure to irritating factors which, as the years go by, become more and more varied, and are made in ever larger quantities.

On studying the literature on occupational and environmental factors, we find that uranium and its substitutes, chromates, nickel, beryllium, and some carcinogenic hydrocarbons are chiefly incriminated. These are all substances of frequent use in industry. We also find a good deal of pulmonary cancer among men working with asbestos in mines where pneumoconiosis occurs. Yet we must acknowledge that the causal relation is seldom fully established.

Hammond and Machle (1956) have accepted, as we all do, a connexion between cigarette smoking and lung cancer, yet we must admit that the first approach to this problem was only conjectural. Hammond and Horn (1958) made an enquiry in 1954 bearing on 187,783 men, of whom 4,854 died within approximately twenty months from the time they were questioned. According to the death certificates, 844 were due to cancer, of which 167 were attributed to primary cancer of the lung. Then, Doll and Hill (1950) made a preliminary report on a similar study of 24,389 British physicians, aged 35 and over, and followed for twenty-nine months (Table II, from Mayer and Maier, 1956).

TABLE II.—SUMMARY OF FINDINGS REPORTED BY 14 RETROSPECTIVE CLINICAL STUDIES ON THE ASSOCIATION OF SMOKING AND LUNG CANCER

| | | No. of cases | | % who were non-smokers among those | | % who were heavy smokers among those | | Relative risk of lung cancer | |
|---|---|---|---|---|---|---|---|---|---|
| Country | Date | with lung cancer | without lung cancer | with lung cancer | without lung cancer | with lung cancer | without lung cancer | All smokers | Heavy smokers |
| Ger. | 1939 | 86 | 86 | 3·5 | 16·3 | 50 | 10·5 | 5·4 | 22·2 |
| Ger. | 1943 | 93 | 270 | 3·2 | 15·9 | 31·2 | 9·3 | 5·7 | 16·7 |
| Neth. | 1948 | 136 | 100 | 5 | 19 | 55 | 19 | 4·5 | 11 |
| U.S. | 1950 | 82 | 522 | 14·6 | 23·9 | 18·3 | 9·2 | 1·8 | 3·3 |
| U.S. | 1950 | 444 | 430 | 7·2 | 30·4 | — | — | 5·6 | — |
| U.S. | 1950 | 605 | 780 | 1·3 | 14·6 | 51·2 | 19·1 | 13 | 30·1 |
| Eng. | 1952 | 93 | 186 | 5·4 | 6·5 | 38·5 | 23·8 | 1·2 | 1·9 |
| Eng. | 1952 | 1357 | 1357 | 0·5 | 4·5 | 25 | 13·4 | 9·4 | 16·8 |
| U.S. | 1953 | 63 | 133 | 4·1 | 20·6 | 67·6 | 29·3 | 6·1 | 11·6 |
| U.S. | 1953 | 477 | 615 | 3·8 | 13·2 | 46·8 | 30·7 | 3·8 | 5·3 |
| Fin. | 1953 | 728 | 300 | 0·6 | 18 | 65·8 | 20 | 36·4 | 79 |
| U.S. | 1954 | 518 | 518 | 3·7 | 10·8 | 75·6 | 44·2 | 3·2 | 5 |
| U.S. | 1954 | 490 | 2365 | 8 | 26·9 | 52·7 | 22·7 | 4·2 | 7·8 |
| U.S. | 1954 | 265 | 287 | 1·9 | 9·7 | 73 | 57 | 5·5 | 6·5 |

We see that an association between cigarette smoking and cancer has been difficult to bring out clearly, even though no one to-day would deny its existence and importance. We are of the opinion that cigarette smoking is one of the causal factors in the development of lung cancer, but that its relationship may not be a simple one.

### GENERAL ATMOSPHERIC POLLUTION

Only a small proportion of our population is employed in factories or industrial firms where there is a considerable risk of contracting lung cancer. But the whole population inhales the air which is polluted in various degree by many organic substances. Most of the pollution is from soot, smoke from coal and fuel oil and fumes from motor cars or tarred roads. In general, whenever an organic material is heated, carcinogenic elements are liable to be introduced into the atmosphere, either by distillation, or following cracking or burning. In combustion, hydrocarbons yield a great variety of substances which tend to concentrate on cooling and Campbell and Kreyberg (1956) have used the benzpyrene content as an indicator of hydrocarbon pollution.

The same point could, of course, be made about radio-active substances. These were comparatively rare some fifteen years ago, before the present vast production of radio-isotopes for military and scientific purposes got into its stride. Factories dealing with thousands of tons of uranium must, surely, be sources of activity, whatever the proportion of air-scatter from them may be. Nevertheless, systematic analyses show that the cancer rate of the general population is comparatively little increased from this particular source.

We thought it might be interesting to show a record of five years in the life-history of 500 pulmonary cancer cases living in a city in which the distribution of airborne dust is fairly well known. In Fig. 6 we have plotted the place of residence of known cancer patients on the map of the Liège area, and the valley joining it from the south-east. Generally it would appear (Fig. 6) that the houses of cancer patients are largely concentrated in the centre of the city, stopped by the hill bordering the city in the north, extend eastward, north-east, and some south-east. But if we look in detail at that distribution of dwellings, we see some interesting facts. Many workers are busy in the huge metallurgic establishments just upstream of the City (Cockerill and Ongare). These workers live in dwellings which were built for them about ten to fifteen years ago. Because of the prevailing wind, the area which they all occupy is one of the least polluted by chemical dust. Yet the number of pulmonary cancers is fairly large. In contrast, in the centre of the area which is surrounded by a horseshoe of the Meuse, immediately north-east of the first

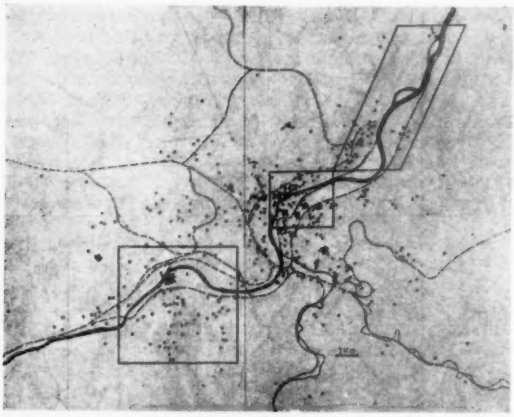


FIG. 6.—Map of the City of Liège and outskirts with in black points all the residence of the patients affected with lung cancer during the last five years (1952–1957).

area, there are few cancer patients, even though this is a sort of tableland on which dust is rather abundant. But there is no industry on the plateau and it has been a pleasant residential area for about forty-five years with many trees and occupied by the well-to-do middle class. The high dust pollution of this area was, of course, not known at the time it was built.

We have been struck by the large number of persons with cancer living in the centre of the city and especially in streets beside railways or canals carrying coal-burning boats. Our attention is drawn to these by their names, "Rue de la Gare, Rue de la Station, Rue du Chemin de fer, Rue du Vincinal". Railway engines are an obvious source of air pollution and steamboats also clearly pollute the air around docks. These sources have been emphasized recently in Canada. During 1955 the incidence of lung cancer was found to be five times higher among engine drivers than among the whole population in the same neighbourhood. Engine drivers of course inhale carcinogenic hydrocarbons either from the sooty exhaust of diesel engines or the smoke of coal-burning locomotives.

In Belgium, too, we can see a striking correspondence between smoke and lung cancer. In the vicinity of factories in Herstal, including the famous Belgian Fabrique Nationale, one can find many men out of work because of cancer. But as the valley runs north the incidence suddenly drops and, at the same time, the smoke disappears and the sky assumes the lovely milky hue it shows in Holland and which has been rendered famous by the Dutch painters of the eighteenth century. Towards the east the smoke continues and with it the cancer.

From our five years of research we must conclude that lung cancer has a complex ætiology. Of several causes cigarette smoking is a very important, but not always an essential, one. Indeed, it seems to us that polluted air, and particularly the hydrocarbons contained in soot, remains the most important cause.

## BIBLIOGRAPHY


ANDERVONT, H. B. (1939) *Publ. Hlth. Rep., Wash.*, **54,** Pt. 2, 1519.
BLACKLOCK, J. W. S. (1957) *Brit. J. Cancer*, **11,** 181.
CAMPBELL, J. M., and KREYBERG, L. (1956) *Brit. J. Cancer*, **10,** 481.
COMMINS, R. T., WALLER, R. E., and LAWTHER, P. J. (1956) *Brit. med. J.*, ii, 753.
——, ——, —— (1957) *Brit. J. industr. Med.*, **14,** 232.
COOPER, R. L. (1954) *Acta Un. int. Cancr.*, **10,** 102.
CURETON, R. J. R., and HILL, I. M. (1955) *Thorax*, **10,** 131.
DOLL, R., and HILL, A. B. (1950) *Brit. med. J.*, ii, 739.
DUNGAL, N. (1946) *Amer. J. Path.*, **22,** 737.
FIRKET, J. (1931) *Bull. Acad. R. Méd. Belg.*, **11,** 683.
—— (1936) *Trans. Faraday Soc.*, **32,** 184.
——, *et al.* (1935) Monographie. Liège.
HAMMOND, E. C., and HORN, D. (1958) *J. Amer. med. Ass.*, **166,** 1159.
——, and MACHLE, W. (1956) In: Mayer and Maier (1956); p. 41.
KREYBERG, L. (1956) *Brit. J. prev. soc. Med.*, **10,** 145.
LAWTHER, P. J. (1955) *Lancet*, ii, 745.
MAYER, E., and MAIER, H. C., eds. (1956) Pulmonary Carcinoma. New York and London.
NEUBUERGER, K. T., and GEEVER, E. F. (1942) *Arch. Path.*, **33,** 551.
RHOADS, C. P. (1956) In: Mayer and Maier (1956); pp. 3, 458.
SMITH, W. E. (1956) In: Mayer and Maier (1956); p. 12.
STAEHELIN, R. (1919) *Jahreskurse ärztl. Fortbild.*, **10,** 30.
STOCKS, P., and CAMPBELL, J. M. (1955) *Brit. med. J.*, ii, 923.
TUYNS, A. (1954) *J. belge Radiol.*, **37,** 283.
WALLER, R. E., and LAWTHER, P. J. (1955) *Brit. med. J.*, ii, 1356.
——, —— (1957) *Brit. med. J.*, ii, 1473.

# Section of Medicine

President—W. A. BOURNE, M.A., M.D., F.R.C.P.

[*January* 28, 1958]

## DISCUSSION ON SEDATION AND STIMULATION OF MAN

**Dr. William Sargant** (London):

The value of a physical approach to the healing of the spirit of man, as well as to the healing of his body, has been demonstrated beyond any shadow of doubt in recent years. In the last quarter of a century we have, in fact, watched a whole range of psychiatric syndromes and their treatments being taken over, lock, stock and barrel, from psychiatry by general medicine, and many syndromes have certainly proved themselves to be much more efficiently treated by the mechanistic methods of modern medicine, and along mainly physiological lines. The conquest of G.P.I. with penicillin, the abolition of pellagrous madness with nicotinic acid, all the mental states responding to recently synthesized vitamins and endocrines, and now the success attending the use of insulin, E.C.T., leucotomy and the like, are all examples of this. It should not, therefore, be at all surprising to find that very few patients to-day ever reach psychiatrists without physicians or surgeons first also having attempted to influence the mind with some form or other of sedative or stimulant drug, and that we are now using so many more and varied types of drugs for such purposes.

There are many people, however, who feel that the chemical treatment of the mind is something morally discreditable, and certainly not to be encouraged—except perhaps for the purpose of getting other people to pay as much in taxes as possible. And we certainly cannot ignore all the heavy overtones of ethics and morality which constantly burden discussions of this nature. I am sure that among my readers will be found some who feel that the provision of courage, will-power, and freedom from anxiety by means of bottles of medicine or pills is very wrong indeed. This is a problem which must be faced straightaway. World Health Organizations and other detached and often well-meaning bodies, and individuals, may continue to deplore the increasing use of various sedative drugs and tranquillizers, and certain persons, obsessed with their own great power of self-control, or proud of their remarkable strength of will, may continue to write to medical and other journals, deploring the use of almost any form of sedative or stimulant by man. But the doctor's first and foremost duty is to try to treat his patient in as efficient and practical a manner as possible, and to help to the best of his ability those coming to him for relief of often intolerable and incapacitating nervous symptoms, whether they be psychologically or physiologically determined. It is complete and utter nonsense to say we are a nation becoming medically dependent on chemical aids to the attainment of spiritual grace. But we are becoming more sensible medically, I think, about the unnecessary, avoidable and often physically exhausting nature of much human mental suffering, which can be so much worse than physical suffering.

My only three months' experience in general practice, obtained in between two of my training posts in psychiatry, showed me, in fact, how many people may be helped by sensible and simple remedies, such as a bottle of bromide or even a double whisky, as opposed to the use of skilled specialized psychiatric talk and religious or moral exhortation. Those who insist on the supreme value and the absolute need for specialized psychotherapeutic treatments of the neuroses are often those who are almost blind to what can be achieved more simply in so many instances by the skilled use of stimulant and sedative drugs. Millions of pounds in pensions were, for instance, saved in World War II simply because it was at last realized that immediate and heavy "front line" sedation was generally more effective in the prevention of chronic neuroses, and of so-called "malingering" reactions, than all the threats of shooting for cowardice and the verbal exhortations and moral punishments used instead as treatments from time immemorial. Both physical and psychotherapeutic methods of treatment are, of course, best combined in many patients. It is important that we always try to use only those drugs which are the least harmful and the best tolerated by the individual, and which do not cause too severe psychological and physiological symptoms when they have to be withdrawn or curtailed.

It is impossible to mention here anything more than a fraction of the numerous sedatives and stimulants now available for treating the mind of man. I shall try to keep mainly to some important general principles of their use. In considering the increasing range of chemical aids to sedation and stimulation, we can easily find ourselves becoming very bewildered and confused. For chemical manufacturers are now producing and advertising extensively many new drugs, and many new combinations of new and old drugs; and so

many drugs are given a succession of new trade names, and so many impressive trade names are being attached to sometimes old and quite worthless remedies that all this may lead to a state of medical and lay drug intoxication and confusion, which will almost certainly result in doctors giving up, wrongly, some of the still valuable older drugs, and passing over other valuable newer drugs. For example, I believe that the initial advertising and claims for chlorpromazine, and the pressing of its use on the general practitioner, long before most psychiatrists in this country had any chance to test it out in specialized centres, nearly resulted in its being discredited and given up in many quarters. It has proved eventually to be a valuable, even if limited, new sedative drug. But it is only now, some four years after its introduction, that many of us are starting to learn how to use this drug properly, in part because of all the early claims and counter-claims that so confused the minds of the ordinary doctors and those of many psychiatrists as well.

Another source of possible confusion is the present vogue for the testing of these new drugs by double-blind sampling methods. Such methods can sometimes be a source of as much misinformation as they are of useful information. We may learn, for instance, from such methods that over the whole range of varied neuroses chlorpromazine or Equanil is not much more effective than small doses of Sodium Amytal, and also, incidentally, is very much more expensive to prescribe. But what it may be really important for us to find out is whether or not Amytal can help a particular small group of neuroses better than chlorpromazine can, or whether chlorpromazine helps other small groups which are untouched by Equanil. There is now a tendency to lump too many psychiatric states together in the testing of these new tranquillizers, and this is as bad as was lumping together all fevers in the old days to find out whether or not, for instance, quinine was of any use as a febrifuge. Double-blind sampling tests would probably have led to the finding that quinine was no good at all for fevers in general, and one might then have missed completely the fact that it was indeed of the greatest value in the treatment of malaria.

A point which needs to be emphasized is the importance of the correct dosage. Pavlov showed in his dogs that what he termed the "strong excitatory" dog might need no less than eight times the dose of a sedative drug needed by the "weak inhibitory" dog. He stressed also that if drugs were to have their best therapeutic effects in relieving the experimental neuroses he induced in his animals, correct dosage was of the utmost importance; to give a "strong excitatory" dog the "weak inhibitory" dose of any drug was absolutely useless, and to give the "weak inhibitory" dog the dose needed by a "strong excitatory" animal was to make its neurotic condition much worse rather than any better. Experience in psychiatry has confirmed the importance of Pavlov's observations, which are equally applicable to man. There are just as many various types and constitutions in human beings as there are in dogs, and these constitutional types are very differently tolerant of the same doses of a drug. Some of our schizophrenic patients, for instance, are walking about and greatly benefiting from being treated with over 600 mg. of chlorpromazine a day, and are being little upset by such large doses. Other patients with hysterical illnesses may fall about and be worsened by taking only 25 mg. of the same drug three times a day. We all know the strong excitatory businessman who is only mildly sedated with half a bottle of whisky, and who merely laughs at a capsule of Sodium Amytal as a sedative; his weaker inhibitory colleague, on the other hand, may be made quite drunk by a capsule of Sodium Amytal, and would have a hangover for many hours from a dose of whisky taken merely as a mild stimulant by his stronger and more forceful colleague. It is these varied medical and constitutional considerations, which are always with us, that may lead us astray in our endeavours to find the proper uses and dosages of new drugs.

Subject to many provisos, one can say that the last quarter of a century has shown us some valuable apparent progress in trying to find more satisfactory chemical sedatives and stimulants for man. Whether many of the newer ones are really very much better than the old ones cannot, however, yet be said with absolute certainty. Fashion and authority in drug prescribing may certainly change in the most startling way. I was trained at St. Mary's and in the school of the late Sir William Willcox. At that time the giving of any barbiturates at all was considered a major therapeutic crime. This did, however, give one the opportunity of exploring the value of several other drugs and sedatives. One learned, for instance, the value of very large doses of aspirin, given both as a sedative and pain-reliever, and how effective this could be in some patients. Though I played a part in bringing to light the amount of bromide intoxication occurring at a time around 1936, when bromide was about the fourth most widely prescribed drug under the old panel system, and this helped towards its present disuse and discredit, nevertheless there are still certain patients who seem to be helped by bromide perhaps more effectively than by many of the newer or older tranquillizing drugs. Obsessive tension states seen in the human, and possibly equivalent to some of Pavlov's stronger excitatory states in dogs, are often very poorly helped by barbiturates. If such people take barbiturates in reasonable doses they may obtain very little benefit; small amounts of

barbiturates may even make these patients more excited and tense rather than relieve any of their anxiety. Addiction to much larger doses of barbiturates may, alternatively, develop. Other explosive personality types sometimes have equally unfortunate reactions when small doses of barbiturates are prescribed. I believe there is still a field for the use of bromides in some tension states. It is certainly difficult to believe that the enormous amounts of bromide used for so many years, both in psychiatry and in general medicine, were of no value at all, although this drug has now become almost totally discredited.

Turning to the barbiturates, they are perhaps the most effective routine sedative we have at our disposal for the majority of our neurotic patients. Especially in the neuroses they are undoubtedly as efficacious in the general run of patients as are the newer tranquillizers, such as Largactil and Equanil; the trouble is they are often too efficacious. The fact is they not only relieve anxiety but also create pleasant states of euphoria, and it is this euphoria which increases the tendency to undesirable addiction. In rebellion against some of the absurdities of my St. Mary's teaching on sedatives, I was one of the first persons to advocate a much wider general use of the short-acting barbiturates as a routine sedative. In the first edition of my book with Eliot Slater "An Introduction to Physical Methods of Treatment in Psychiatry", in 1944, I made the statement that these barbiturates, in moderate doses, did not cause addiction in the true sense of the word, nor severe symptoms on withdrawal. But I think this statement has now to be modified. For I, with others, have come to realize that patients with chronic tension states may continue to remain tense and anxious for many years, because they are, in fact, suffering more from a self-induced or doctor-induced chronic barbiturate tension state than from a persisting anxiety neurosis *per se*. I am now seeing patients who have had one, two, or even three leucotomies performed for a chronic persisting tension, and who have then turned out to be, probably, cases of chronic barbiturate addiction. If they can be weaned from their barbiturates, their tension may still resolve, even after the failure of their leucotomies to help them. One sees fewer of these patients addicted to the longer-acting barbiturates, such as phenobarbitone and sol. barbitone. These two drugs are, of course, not so efficacious in regard to the temporary relief of tension as the short-acting barbiturates, and they also create much less euphoria which is such an addicting quality in any drug. The new tranquillizers, such as Largactil and Equanil, also do not create such undesirable states of euphoria in the neuroses. But they may also be less effective in bringing relief of anxiety in many neuroses, despite Largactil proving to be so valuable in the treatment of some acute and chronic psychotic patients. Equanil can produce some very favourable results indeed in selected neuroses, but it is still difficult to find out exactly which groups of neuroses are most helped. I have gained the impression, however, that it is the patient showing mixed obsessive and hysterical symptoms who is often helped by Equanil in the clinical dosage usually prescribed. Equanil also seems to be of considerable help in alcoholic withdrawal states. Severe obsessional states are not generally helped by either of these two new drugs. The great danger of another new drug—Serpasil—in the neuroses is that it can produce such severe states of near-psychotic depression. Undoubtedly many suicides have been caused because general practitioners were persuaded into using it in patients with neuroses and early psychoses, and normals with hypertension, before these and other complications of the drug had been discovered by trials in expert hands.

I feel myself quite unable to discuss many of the new tranquillizers that have recently been introduced. It may take one several years to learn how to use a new drug properly and skilfully, and I think the only hope for all of us at the present time is to try to stick to a limited range of drugs, both new and old, and to concentrate on trying to master the proper use of a few drugs, rather than to play around ineffectively with too many. For instance, one should learn how to handle a good short-acting barbiturate, a medium, and a long-acting one; these together with one or two of the new tranquillizers, such as Largactil and Equanil, will prove to be a fairly satisfactory range of sedatives to use in clinical practice at the present time for neurotic and normal patients.

Turning for a moment to the sedation of psychotic patients, many of our problems arise also from ignorance as to the correct dosages to be administered to our varied groups of patients, and we know as yet little about the length of time drugs need to be given to obtain the best results. We have seen this recently in the treatment of schizophrenia by Largactil. Originally much poorer results were being obtained in England with this drug because it was not always realized that very much larger doses were often needed in the treatment of schizophrenia than in normal persons or neurotics. Maintenance doses of from 400 to 800 mg. a day may be needed to help some patients, who may get about or go back to work on such doses. But the use of similar amounts in severe depressive illnesses might well drive a patient to suicide by greatly increasing the depressive features present. And one must be very guarded indeed in ever using Serpasil in patients with a history of previous psychotic or neurotic depression, while being prepared to use it, if necessary, in very large doses in the sedation of schizophrenia. What we do not know yet is how long such drugs have to be kept on in

patients in whom these drugs appear to be helping to hold at bay a schizophrenic illness. Some of us have had patients on Largactil for months or years already, with an ever-present danger of relapse when the dosage is stopped or lowered. But such findings do suggest that we may be on the verge of new and exciting developments in the more practical biochemical treatment and handling of some schizophrenic and other psychotic patients.

It is unfortunate that much less effective stimulants than sedatives have so far been developed. Again we are also seeing more addiction than we used to with amphetamine drugs, but it is still very much less than with the barbiturates. This is often because the taking of too much Benzedrine creates sleeplessness, and those searching for euphoria and temporary oblivion do not appreciate too many long nights without sleep. However, one must recognize those states of paranoid confusion which result from the taking of Benzedrine in too large a dosage and for too long a time. This can precipitate people suddenly into mental hospitals, often quite wrongly diagnosed as schizophrenics; the symptoms, however, clear up rapidly when the drug is withdrawn. We have also learned how ineffective amphetamine and allied drugs are in the treatment of any but mild cases of depression. The only advantage of some of the recent substitutes, such as Preludin and Meratran, has been in the absence of some of the side-effects which Benzedrine often produces. But Meratran itself in very small doses can occasionally cause severe and most unpleasant temporary psychotic complications.

I have given only a very rough outline of some of the main principles which seem to be so important in the use of sedatives and stimulants in man. May I end with a plea that, in using the ever-increasing range of new drugs, we do not rush too madly from one set of new drugs to another. Let us look around and see where the main gaps are in our present therapeutic armamentarium, and try to encourage the development of drugs which will help to fill these treatment gaps first of all. Some advances have been made, I think, in the treatment of anxiety, but very much better drugs are still needed in the treatment of obsessional states and depressive reactions; and we are also looking out for new and better sedative drugs in the treatment of the schizophrenias. We must not be too ready to abandon the old for the new, until we have learned how to use the new skilfully and economically, and in centres properly equipped to test them out. This will help to avoid some of the real disasters we have seen in recent years in the too hasty foisting of new tranquillizers on to the general practitioner and public alike.

Finally, let us remember that well-known prayer for "all sorts and conditions of men"; and let us not forget that all of these people will need very different types and strengths of sedation and stimulation, if they are to obtain the help they so often ask of us to-day. Let us never make the mistake of thinking that there will be any real short-cuts or cheap universal remedies in the skilled chemical treatment of the spirit of man.

**Professor E. J. Wayne** (Glasgow):

I have assumed that it is my special task to deal with the pharmacological background of this subject and I intend in addition to examine critically the results reported by clinicians on the use of drugs which sedate and stimulate man.

Early in his history man recognized the effect of two naturally occurring drugs, alcohol and caffeine, which he still consumes in vast quantities. Any satisfactory depressant or stimulant drug must be more effective or have fewer side-effects than these and should preferably be at least as cheap. Since states of over-activity and nervous tension are more common than states of depression I intend to deal first and more fully with the sedative group of drugs. Alcohol's earliest competitor was phenobarbitone and this drug is still widely used. It is probable that most hypnotics act as sedatives when given in small doses and the short acting hypnotics such as amylobarbitone are very effective daytime sedatives when given in this way. With the introduction of the antihistamines, the opinion that sedation could be produced only by substances which in larger doses caused first sleep and then anæsthesia was found to be incorrect. In both animals and man these drugs in small doses have a sedative effect and in larger doses produce drowsiness while even in lethal doses anæsthesia is not produced.

A feature of recent pharmacological work has been the search for drugs which will relieve anxiety and tension without impairing clarity of thought or initiative. The idea of a tranquillizing drug came many years ago to Aldous Huxley when he described in "Brave New World" his hypothetical substance "soma". Observations on animals lend support to the view that there probably are drugs of this kind which tranquillize without causing sleep. Thus a substance such as reserpine may convert wild jungle-bred monkeys into calm and unafraid animals. Jacobsen and Sonne (1955) have described methods of producing experimental neuroses in animals and have shown that benactyzine may diminish conflict-induced symptoms. Thus, for example, a rat which expects the sound of a buzzer to precede a mild electric shock stiffens into a characteristic position whenever it hears this noise. Re-

treatment with a tranquillizer may render the animal indifferent to the stimulus. Electrical stimulation of the hypothalamic area may be used to produce outbursts of sham rage which can be prevented by drugs such as reserpine and chlorpromazine.

The mechanisms by which these drugs produce their effect is obscure, mainly because we still know comparatively little about the chemical transmitters in the central nervous system. There is some evidence, however, that acetylcholine, noradrenaline and 5-hydroxytryptamine (5 HT) may all play a part in central transmission. It is tempting to link the action of reserpine with the fall in hypothalamic noradrenaline content which can be shown to occur when reserpine is injected. It has also been suggested that reserpine may act through the release of 5 HT since this substance on injection into the cerebral ventricles of cats causes, like reserpine, loss of energy and signs of lethargy. The hypothesis is supported by the fact that 5 HT antagonizes lysergic acid diethylamide (LSD) a potent hallucinogen resembling mescaline in its pharmacological effects, both reproducing some of the mental phenomena associated with schizophrenia. The more recently introduced compound azacyclonal (Frenquel) has been shown to correct the electroencephalographic changes induced in animals by LSD and mescaline and to abolish the experimental psychosis produced in humans by these substances. Several of the tranquillizing drugs, e.g. benactyzine, are powerful anticholinergic agents but other anticholinergic substances such as atropine do not tranquillize, possibly because they are unable to penetrate to receptor sites. It has been suggested that benactyzine blocks pathways between the cortex and lower levels of the central nervous system. These pharmacological aspects have been well reviewed by Lewis (1958).

It is thus clear that our knowledge of both the nature of the chemical transmitters in the central nervous system and also of the effect of drugs upon them is too small to enable clear-cut statements to be made. Nevertheless, the speculations these ideas have produced have already been fruitful in producing many new sedatives.

It is against this background that these newer tranquillizing drugs must be assessed. They may be divided into two main groups roughly corresponding to their main use in psychiatric states. The first group which includes chlorpromazine, promazine, reserpine and azacyclonal are of value in some psychoses and especially in schizophrenia, mania, senility and children's behaviour disorders. They have also been used with some success in the management of drug addiction, in the control of nausea, vomiting and hiccup and to potentiate analgesics especially in the terminal stages of malignant disease. The balance of evidence is strongly in favour of their therapeutic activity and the only objection to their use is the incidence of side-effects. This is greatest with chlorpromazine and reserpine. Promazine seems to have fewer untoward actions but has been in use for a much shorter time. Azacyclonal is a relatively safe drug but is mainly of value in the treatment of hallucinated patients and by no means all of these respond to it.

The second group of sedative drugs consists of those which are used predominantly in the treatment of the neuroses. Methylpentynol when first introduced was thought to produce sedation without clouding of consciousness but has proved a disappointing drug. Its action is very like that of alcohol and it may give rise to a variety of side-effects. Goulding *et al.* (1957) could not distinguish it from inert mixtures when given in a double-blind trial to children before dental operations. From a pharmacological point of view the actions of the other members of the group are dissimilar but in man they all act as depressants. The most widely used is probably meprobamate which is alleged to relieve fear and anxiety. In the U.S.A. 50 tons a month are consumed, equivalent to 150 million tablets a year costing £2,200,000. Meprobamate has an action similar to that of mephenesin in that it blocks multineuronal reflexes and so relaxes muscular tone. The use of both these drugs as sedatives is based on the view that if in anxiety the degree of muscular tension is relieved there will be a corresponding reduction in psychological tension. There is no evidence for this view and I believe it to be fallacious. In the case of mephenesin a carefully controlled clinical trial by Wolf and Pinsky (1954) showed that it was no more effective than inert tablets in relieving either the subjective or objective manifestations of anxiety and tension. In so far as meprobamate produces its effects through its action as a muscle relaxant it is no more likely than mephenesin to be effective in anxiety states. Its sedative properties are due to a direct action on the cortex not unlike that of the barbiturates. At least three properly controlled clinical trials have been carried out by West and da Fonseca (1956), by Raymond *et al.* (1957) and by Lasagna (1956). The most probable conclusion to be drawn from this and other evidence is that meprobamate is a moderately active sedative of no greater clinical value than amylobarbitone or phenobarbitone. It has the merit of being relatively useless as an agent for committing suicide but its side-effects are many and include hypotension, an itching erythematous rash and, more seriously, purpura. Benactyzine is undoubtedly an active drug when tested on animals and produces symptoms in normal human subjects as well as altering the electroencephalogram. It is therefore somewhat surprising that the balance of clinical evidence is so unfavourable. It ranked no better than inert tablets in several well-controlled clinical trials, those,

for example, reported by Seager and Leitch (1956), Raymond *et al.* (1957), Forbes and Earle (1957) and Coadby and Jewesbury (1956). Raymond and Lucas (1956) and Hargreaves *et al.* (1957), on the other hand, found a greater proportion of patients improved on benactyzine therapy than when control tablets were being given.

The design of some of these trials has been criticized but it is clear that benactyzine is at best a feeble sedative. Minor side-effects such as dizziness are frequent but serious ones are rare. The evidence for the value of two other aspirants to this group of tranquillizers, Covatin and hydroxyzine (Atarax) is not impressive. Taking all the reports together it can be said that when allowance is made for the 35% of any population which responds favourably to any form of therapy including inert tablets (Beecher, 1955) there is little evidence that this group of tranquillizers includes many very active drugs. When they are active they do not appear to be greatly preferable to those barbiturates which are conventionally used in the neuroses. Part of their effect in ordinary practice may be due to a transference from doctor to patient of enthusiasm created by the singularly unrestrained advertising adopted by the manufacturers of some of these remedies.

The place of stimulants in the treatment of psychiatric symptoms is much smaller. We already possess three effective compounds: amphetamine, dexamphetamine and methylamphetamine. There is probably little to choose between them and there is no satisfactory basis for the custom of using dexamphetamine in the treatment of obesity and reserving amphetamine for use in depressive states. There are four newcomers to this field: Mephine is another sympathomimetic amine which is said without much evidence to be less liable to produce anorexia than the amphetamines. Preludin is recommended by its manufacturers for the treatment of obesity and is said not to produce excessive mental stimulation. In fact, however, it is a powerful mental stimulant similar in its effects to amphetamine (Randell, 1957) and it has already been shown to give rise to addiction (Bethell, 1957). On the other hand pipradrol (Meratran) is claimed to be a cerebral stimulant which does not interfere with appetite or nocturnal sleep. Nevertheless Begg and Reid (1956) found some interference with sleep although not with appetite. Gelvin *et al.* (1955) on the other hand were able to demonstrate loss of weight in patients receiving pipradrol when compared with a similar group receiving inert tablets. Houston (1956) found pipradrol no more effective than inert tablets in the treatment of a group of chronic retarded schizophrenics. Methyl phenidate (Ritalin) is chemically and pharmacologically similar to pipradrol. On the whole it seems probable that these newer compounds have comparatively little advantage over the older and better tried remedies but pipradrol may prove to have fewer side-effects than the amphetamines.

Mixtures of sedative and stimulant drugs are widely used especially in general practice and no fewer than seven of these are commercially available. Their use is not wholly illogical since they do not completely cancel one another's effect. Many of us drink strong black coffee after a dinner during which we have enjoyed wine, and it would be idle to pretend that the end-result is the same as if we had taken neither. The objection to these mixtures is the general one that it is rarely possible to mix antagonistic drugs in proportions which will suit every case. In addition they are especially liable to cause addiction. They are better avoided.

It cannot be said that the perfect drug for use in abnormal mental states has yet been discovered and, apart from promazine and reserpine, it is still doubtful if the newcomers to this field have any substantial advantage over well-tested drugs such as the barbiturates and amphetamine. It would be a mistake, however, to be too pessimistic and the time may well be at hand when we are able to tone down the patient's anxiety or tension without impairing his initiative or mental lucidity. Alternatively we may be able to rouse him from his torpor and depression without at the same time producing anorexia and insomnia.

## REFERENCES


Beecher, H. K. (1955) *J. Amer. med. Ass.*, **159**, 1602.
Begg, W. G. A., and Reid, A. A. (1956) *Brit. med. J.*, i, 946.
Bethell, M. F. (1957) *Brit. med. J.*, i, 30.
Coadby, A., and Jewesbury, E. C. O. (1956) *Brit. med. J.*, i, 485.
Forbes, H. S., and Earle, B. V. (1957) *Brit. med. J.*, i, 226.
Gelvin, E. P., McGavack, T. H., and Pogge, R. C. (1955) *Clin. Res. Proc.*, **3**, 40.
Goulding, R., Helliwell, P. J., Kerr, A. C., and Wilkin, E. M. (1957) *Brit. med. J.*, i, 855.
Hargreaves, G. R., Hamilton, M., and Roberts, J. M. (1957) *Brit. med. J.*, i, 306.
Houston, F. (1956) *Brit. med. J.*, i, 949.
Jacobsen, E., and Sonne, E. (1955) *Acta pharm. tox. Kbh.*, **11**, 135.
Lasagna, L. (1956) *J. chron. Dis.*, **3**, 122.
Lewis, J. J. (1958) *Topics in Psychiatry*. (In press.)
Randell, J. B. (1957) *Brit. med. J.*, ii, 508.
Raymond, M. J., and Lucas, C. J. (1956) *Brit. med. J.*, i, 952.
——, ——, Beesley, M. L., O'Connell, B. A., and Roberts, J. A. F. (1957) *Brit. med. J.*, ii, 53.
Seager, C. P., and Leitch, A. (1956) *Brit. med. J.*, ii, 1407.
West, E. D., and da Fonseca, A. F. (1956) *Brit. med. J.*, ii, 1206.
Wolf, S., and Pinsky, R. V. (1954) *J. Amer. med. Ass.*, **155**, 339.

# Section of Endocrinology

President—C. N. ARMSTRONG, M.D., F.R.C.P.

[*January* 22, 1958]

## DISCUSSION ON ENDOCRINE CHANGES IN LIVER DISEASE

**Dr. Sheila Sherlock** (London):

THE liver cells play an important part in the metabolism of almost all the hormones by changing the structure, by conjugation (often as a glucuronide) and so rendering them biologically inactive, and by excretion into the bile. In addition, most of the steroid hormones undergo an entero-hepatic circulation in similar fashion to the bile acids. The changes I shall describe are associated with damage to liver cells and are almost exclusively found in chronic disease (Laennec's cirrhosis). Acute hepatitis is too short an illness for such changes to appear and in biliary obstruction the liver cells function well until terminally.

In cirrhosis vascular spiders are found in the vascular territory of the superior vena cava and very rarely below a line joining the nipples. "White spots" are often associated with spiders (Martini and Staubesand, 1953). They appear on cooling the skin and on the arms and buttocks. Examination with a lens shows that at the centre of each is the beginnings of a spider. Erythema of palms and soles is an exaggeration of the ordinary speckled mottling. These three skin changes have been attributed to hyperœstrogenism for there is evidence that the liver conjugates and inactivates œstrogens, for instance from *in vitro* studies in human liver (Tagnon *et al.*, 1952). Patients with cirrhosis have impaired œstrogen tolerance (Glass *et al.*, 1944). Bio-assay and chemical methods have sometimes shown an increased urinary output of œstrogens in liver disease which does not always correlate with the presence of vascular spiders (Cameron, 1957). Vascular spiders are also found in pregnancy (Bean, 1953). Oestrogens have a dilator effect on the spiral arteries of the endometrium and this might be considered analogous to the development of spiders. They have been induced by œstrogen administration (Bean, 1945) but men receiving œstrogen treatment for prostatic carcinoma do not develop them. Against a hormonal cause are the distribution, and random disappearance of one and simultaneous appearance of another. They have been related by others to increased peripheral blood flow, but we could not relate them to the increased cardiac output often found in cirrhosis (Murray *et al.*, 1958). We must conclude that these skin changes cannot be definitely related to œstrogen excess. Other changes in liver disease have also been attributed to hyperœstrogenism, with consequent secondary pituitary depression. They are specially notable in men, perhaps because women developing clinically evident cirrhosis are often post-menopausal. The changes include testicular atrophy with loss of libido, impotence, sterility, prostatic atrophy and disappearance of secondary sexual hair. Low urinary 17-ketosteroid excretion in liver disease was first described by Fraser *et al.* (1941). This might be related to the secondary depression of the testis but decreased metabolism of testosterone has also been postulated (West *et al.*, 1951) but not confirmed (Williams *et al.*, 1951).

Gynæcomastia is a feature particularly of cirrhosis in alcoholics. It may be due to œstrogenization or œstrogen-androgen imbalance but can also be related to malnutrition. It is particularly conspicuous in alcoholics who are malnourished and less obvious in the post-hepatitic type of cirrhosis seen in this country. An analogy can be drawn to undernourished prisoners of war who developed gynæcomastia when they were re-fed and gaining weight (Klatskin *et al.*, 1947).

The liver plays a central role in the metabolism of adrenocortical steroids. Subjects given intravenous $C^{14}$-labelled hydrocortisone show a lower level in the hepatic vein than in an artery, suggesting that the liver is removing the hormone from the peripheral blood (Plager *et al.*, 1954).

Hepatic disease is often stated to cause dwarfing (Day, 1953; Gregory, 1954) secondary to malnutrition, but I have seen only one girl in whom chronic liver disease might be said to have caused dwarfing and this patient came of short parents. I have plotted the stature of girls with cirrhosis against their age. Until about 10 years the height is near the normal mean; from 11 to 14 years in the majority it exceeds that of 90% of the population in that age group according to Tanner's tables (Tanner, 1958). This may represent an augmented "adolescent growth spurt" (Tanner, 1955). Allowing for ascites and œdema the tall girls

were usually also over-weight. Bone age, based on only a limited number of hand and elbow X-rays, seems within the normal range. Sexual maturation is also normal, although these girls as a group have amenorrhœa or irregular, scanty menses. Urinary 17-ketosteroid excretions are low. Even in normal children, the "adolescent growth spurt" is unexplained and in children with cirrhosis the mechanism is also speculative. It has been attributed to increased androgen production; failure of the liver to inactivate this and/or growth hormone remains possible.

My failure to demonstrate a similar growth curve for boys with cirrhosis emphasizes the interesting sex difference in frequency (Table I). Up to 11 years the frequency is about

TABLE I.—JUVENILE CIRRHOSIS (<21 YEARS)

| Type | History hepatitis: Yes | History hepatitis: No | Mean age | Male | Female |
|---|---|---|---|---|---|
| Relatively well; Acne, jaundice, S. globulins raised, &c. .. .. .. | 8 | 12 | 15 (9–21) | 3 | 17 |
| Other .. .. .. .. | 8 | 12 | 7 (2–12) | 8 | 12 |

the same (7 boys and 10 girls) but over 10 years and up to 16 the sufferers are predominantly female (2 males, 12 females). Waldenström (1950) drew attention to this type of cirrhosis in young women and it has since been described by Bearn *et al.* (1956). The patients are well-nourished with amenorrhœa, often acne, moon facies, pigmented striæ and rarely hirsuties.

These features suggest hyperadrenalism, and increased urinary corticoids have been found in some sufferers (Bongiovanni and Eisenmenger, 1951). Dr. R. I. S. Bayliss performed a hydrocortisone tolerance test in one patient and although the fasting blood 17-hydroxycorticosteroids were normal, tolerance was impaired. The patients are mildly jaundiced and serum bilirubin values rise at menstruation or after œstrogen administration (Bearn *et al.*, 1956).

The patients have febrile episodes, and sometimes polyarthritis of rheumatoid type. Serum gamma globulins are very high. A relationship to lupus erythematosus has been suggested for, very rarely, the L.E. phenomenon may be seen in the blood (Bearn *et al.*, 1956; Mackay *et al.*, 1956). Auto-immunization to liver cells has been suggested (Mackay *et al.*, 1956) and this is the rationale for steroid therapy. Prednisone is occasionally followed by a decrease in jaundice and a fall in serum globulins. Once started therapy may need to be continued for months or years.

In conclusion, I will state what I believe to be the indications for corticosteroid therapy in liver disease. Fulminant hepatitis proceeding to hepatic coma carries such a bad prognosis that intravenous hydrocortisone (200 mg. daily) should be given. By "buying time" hepatic regeneration may exceed degeneration. The type of virus hepatitis with prolonged jaundice of obstructive type (cholestasis) may be difficult to diagnose from extra-hepatic bile duct obstruction. In such circumstances, a profound fall in serum bilirubin levels after ACTH 40 units twice daily for four days suggests hepatitis (Shaldon and Sherlock, 1957). An indefinite fall is inconclusive. If the serum bilirubin level does decrease the ACTH should be replaced by prednisone and continued well into convalescence. Prolonged prednisone therapy is justified in cirrhotic patients with persistent jaundice and high serum gamma-globulins, on the supposition that the liver lesion might be due to auto-immunization, but there is no concrete evidence that the underlying liver disease is improved. Finally, a case can be made for using steroid therapy for patients with hepatitis in relapse.

## REFERENCES


BEAN, W. B. (1945) *Medicine, Baltimore*, **24,** 243.
—— (1953) *Circulation*, **8,** 117.
BEARN, A. G., KUNKEL, H. G., and SLATER, R. J. (1956) *Amer. J. Med.*, **21,** 3.
BONGIOVANNI, A. M., and EISENMENGER, W. J. (1951) *J. clin. Endocrin.*, **11,** 152.
CAMERON, C. B. (1957) *J. Endocrin.*, **15,** 199.
DAY, R. (1953) In: Pediatrics. 12th edit. Edited by L. E. Holt, Jr. and R. McIntosh. New York; p. 38.
FRASER, R. W., FORBES, A. P., ALBRIGHT, F., SULKOWITCH, H., and REIFENSTEIN, E. C. (1941) *J. clin. Endocrin.*, **1,** 234.
GLASS, S. J., EDMONDSON, H. A., and SOLL, S. N. (1944) *J. clin. Endocrin.*, **4,** 54.
GREGORY, H. H. C. (1954). In: Diseases of Infancy and Childhood. Edited Parsons and Barling. London; Vol. 1, p. 687.
KLATSKIN, G., SALTER, W. T., and HUMM, F. D. (1947) *Amer. J. med. Sci.*, **213,** 19.
MACKAY, I. R., TAFT, L. I., and COWLING, D. C. (1956) *Lancet*, ii, 1323.
MARTINI, G. A., and STAUBESAND, J. (1953) *Virchows Arch.*, **324,** 147.
MURRAY, J. F., DAWSON, A. M., and SHERLOCK, S. (1958) *Amer. J. Med.*, **24,** 358.

PLAGER, J. E., TYLER, F. H., HECHT, H. H., and SAMUELS, L. T. (1954) *J. clin. Endocrin.*, **14**, 780.
SHALDON, S., and SHERLOCK, S. (1957) *Brit. med. J.*, ii, 734.
TAGNON, H. J., LIEBERMAN, S., SCHULMAN, P., and BRUNSCHWIG, A. (1952) *J. clin. Invest.*, **31**, 346.
TANNER, J. M. (1955) Growth at Adolescence. Oxford.
—— (1958). In: Modern Trends in Paediatrics. 2nd series. Edited by A. Holzel and J. P. M. Tizard. London; p. 325.
WALDENSTRÖM, J. (1950) Stoffwechs.-Krh. Sonderband: XV. Tagung, Bad Kissingen, p. 8.
WEST, C. D., TYLER, F. H., BROWN, H., and SAMUELS, L. T. (1951) *J. clin. Endocrin.*, **11**, 897.
WILLIAMS, T. L., CANTAROW, A., PASCHKIS, K. E., and HAVENS, W. P., Jr. (1951) *Endocrinology*, 48, 651.

**Dr. J. Lee** and **Dr. G. W. Bisset** (London):

*The Secretion of Neurohypophyseal Hormones in Man with Special Reference to Liver Disease*

An attempt has been made to investigate the secretion of neurohypophyseal hormones in man by assaying oxytocic and antidiuretic activity in blood. ADH is unstable in serum and it is now generally accepted that it is essential to use an intravenous technique for the assay of this hormone in body fluids (van Dyke *et al.*, 1955). Oxytocin can be assayed for its milk-ejecting activity in the lactating rabbit, but a more convenient preparation for routine work is the isolated uterus of the rat. It is not practicable, however, to use whole blood or plasma in an assay on an isolated organ because, when plasma comes into contact with glass or is diluted in the organ bath, active polypeptides are released from precursors in the plasma proteins. Other oxytocic substances are also present in blood such as potassium and 5-hydroxy-tryptamine.

In order to eliminate interfering substances and to obtain detectable amounts of activity, concentrated extracts were prepared from human blood by the method of Bisset and Walker (1954, 1957) or in recent work by a modification of that method (Bisset and Lee, 1957*a*). Oxytocic activity was assayed on the isolated uterus of the virgin rat in œstrus (Holton, 1948), and antidiuretic activity by intravenous injection of the extracts into rats under ethanol anæsthesia (Ames and van Dyke, 1952). Samples of the extracts were treated with 0·01 M sodium thioglycollate which inactivates neurohypophyseal hormones (van Dyke *et al.*, 1942). Any activity which was not abolished by this treatment was assumed to be due to an extraneous factor, and excluded from the results. Activity was assayed against oxytocin (Pitocin) or vasopressin (Pitressin).

In extracts of blood collected from the median cubital vein, under conditions of rest, antidiuretic activity was not detectable. Stimulating the neurohypophysis with nicotine was studied. A water diuresis was induced in a subject and then inhibited by smoking. To obtain an estimate of the amount of hormone released from the neurohypophysis, concentrated extracts were prepared from the urine by the method of Noble *et al.* (1939), according to the description given by Taylor and Walker (1951), and assayed for antidiuretic activity. Control experiments were carried out to estimate the recovery of ADH from the blood and from urine, and in order to correlate the results, suitable corrections have been applied to the assays. During the initial diuresis the concentration of antidiuretic activity in the peripheral venous blood was $<0{\cdot}008$ mU/ml. and the total amount excreted in the urine, 1·2 mU. During the period of antidiuresis the corresponding figures were 0·040 mU/ml. and 57 mU. There was no change in the oxytocic activity of the blood before and after smoking. It was found by Noble and Taylor (1953) that when ADH was infused intravenously in man, the mean excretion of hormone in the urine was approximately 13% of the amount infused. Conversely, if 57 mU were excreted in the urine in this experiment it may be assumed that the amount secreted by the neurohypophysis was of the order of 500 mU. Even if this amount were released instantaneously, the concentration in the blood alone could not exceed 0·1 mU/ml. The value actually obtained was 0·040 mU/ml., and this suggested that nicotine did in fact cause the sudden release of a large amount of ADH from the neurohypophysis. Further evidence for this view was obtained from another experiment in which antidiuretic activity was assayed in specimens of urine passed at intervals of fifteen minutes. It is evident from these experiments that, even when a powerful stimulus is applied to the neurohypophysis, the concentration of antidiuretic activity in the blood shows only a transient rise to detectable levels.

Ames *et al.* (1950) were unable to detect antidiuretic activity in blood from the femoral vein of dogs in which the neurohypophysis was stimulated by the intracarotid injection of hypertonic saline, but found that the concentration in blood from the internal jugular vein was as high as 0·5 mU/ml. It was, therefore, decided to assay activity in blood from the internal jugular vein in man. This was done in 11 patients under anæsthesia, prior to surgical operations (Bisset *et al.*, 1956). In control experiments, in which Pitocin or Pitressin was added to blood and extracted, approximately one-third of the activity was recovered. The figures which follow are not corrected for loss of activity on extraction. In 7 cases, the levels

of oxytocic activity were between 1·1 mU/ml. and 2·3 mU/ml., and in 4, antidiuretic activity was detected at levels between 0·012 mU/ml. and 0·025 mU/ml. It seemed possible that these comparatively high levels of activity might have been due to stimulation of the neurohypophysis by anæsthetic drugs.

Through the courtesy of Dr. Sheila Sherlock, it became possible to obtain blood samples from the internal jugular veins of conscious patients, who were undergoing cardiac catheterization as part of a procedure to investigate liver function. At the same time blood was taken from the femoral artery or the median cubital vein. A preliminary series of 6 cases has already been reported (Bisset and Lee, 1957*b*). The number has now been extended to 13. An improved method of extraction was used in these experiments (Bisset and Lee, 1957*b*). The average recovery was 58%. The figures which follow are uncorrected. The mean concentrations of oxytocic and antidiuretic activity in blood from the median cubital vein or the femoral artery were <0·4 mU/ml. and <0·006 mU/ml. respectively; in blood from the internal jugular vein, <0·6 mU/ml. and <0·009 mU/ml. Antidiuretic activity was detected in 5 cases in blood from the internal jugular vein only; the concentrations ranged from 0·005 mU/ml. to 0·025 mU/ml. In 2 cases in which it was possible to make a comparison, the concentration of oxytocic activity in blood from the internal jugular vein was three to six times higher than in blood from the median cubital vein or the femoral artery. A ratio of 6:1 was also obtained in an anæsthetized patient, not recorded in this series. The relatively high concentration of both oxytocic and antidiuretic activities in blood from the internal jugular vein, suggests that these activities are, in fact, due to the hormones of the neurohypophysis.

In the 5 cases in which antidiuretic activity was detected, the patients had fluid retention. However, there were 2 cases with fluid retention without detectable levels of antidiuretic activity. In one the ascitic fluid contained malignant cells and in the other case the œdema was resolving.

From each of the 3 cases with detectable levels of antidiuretic activity, and also from the case with resolving œdema, a twenty-four-hour sample of urine was collected, of which 100 ml. were extracted and assayed for antidiuretic activity. The mean recovery in extractions from urine was 30%. Table I gives the results, which are not corrected for loss of

TABLE I.—LEVELS OF ANTIDIURETIC ACTIVITY IN BLOOD AND URINE

| Antidiuretic activity in blood mU/ml. | Antidiuretic activity in urine mU/100 ml. | Daily urine volume (ml.) | Total antidiuretic activity mU/24 hours |
|---|---|---|---|
| 0·020 | 4·8 | 750 | 36 |
| 0·012 | 2·8 | 900 | 25 |
| 0·005 | 2 | 550 | 11 |
| <0·003 | <1 | 2,200 | — |

Blood was obtained from the internal jugular vein.

activity on extraction. It is of interest to note the correlation between the concentration of antidiuretic activity in central blood and the total amount of antidiuretic activity excreted in the urine.

It is believed that the antidiuretic activity is due to ADH. The levels of oxytocic activity appear to be relatively high, but if the activity is not due to oxytocin, it must be due to some unknown physiological substance which is inactivated by thioglycollic acid. Further work is necessary to establish that the oxytocic activity is due to oxytocin.

## REFERENCES


AMES, R. G., MOORE, D. H., and VAN DYKE, H. B. (1950) *Endocrinology*, **46**, 215.
——, and VAN DYKE, H. B. (1952) *Endocrinology*, **50**, 350.
BISSET, G. W., and LEE, J. (1957*a*) *Lancet*, i, 1173.
——, —— (1957*b*) *Lancet*, ii, 770.
——, ——, and BROMWICH, A. F. (1956) *Lancet*, ii, 1129.
——, and WALKER, J. M. (1954) *J. Physiol.*, **126**, 588.
——, —— (1957) *Brit. J. Pharmacol.*, **12**, 461.
HOLTON, P. (1948) *Brit. J. Pharmacol.*, **3**, 328.
LAUSON, H. D. (1951) *Amer. J. Med.*, **11**, 135.
NOBLE, R. L., RINDERKNECHT, H., and WILLIAMS, P. C. (1939) *J. Physiol.*, **96**, 293.
——, and TAYLOR, N. B. G. (1953) *J. Physiol.*, **122**, 220.
TAYLOR, N. B. G., and WALKER, J. M. (1951) *J. Physiol.*, **113**, 412.
VAN DYKE, H. B., ADAMSONS, K., and ENGEL, S. L. (1955) *Recent Progr. Hormone Res.*, **11**, 1
——, CHOW, B. F., GREEP, R. O., and ROTHEN, A. (1942) *J. Pharmacol.*, **74**, 190.

**Dr. W. H. J. Summerskill** (London):

*Adrenal Steroids and the Liver*

(1) *The metabolism of steroids by the liver.*—With the exception of high levels of urinary aldosterone, especially with ascites, and low concentrations of 17-ketosteroids in the urine, the latter probably reflecting decreased production, there is little clinical or biochemical evidence of abnormal adrenal steroid metabolism in patients with liver disease under normal circumstances. However, infused hydrocortisone disappears more slowly than in the normal subject, impaired metabolism being related to the degree of liver damage in terms of bromsulphthalein retention (Plager *et al.*, 1954). The utilization of cortisone is normal in patients with liver disease, but a block is thought to occur in the enzymatic reduction of hydrocortisone to the tetra compounds (Brown, 1957). The inactivation of orally administered steroids in the liver is probably an important factor in explaining their lower potency in relation to systemic hydrocortisone or ACTH.

The metabolic processes involved in the degradation of aldosterone are unknown, but human liver slices inactivate the salt-retaining fraction from human urine (Chart *et al.*, 1956) and the liver is probably the site of its metabolism.

(2) *Steroid drugs and jaundice.*—The indications for steroid therapy in liver disease have been discussed by Dr. Sherlock, but their contribution to diagnosis should be emphasized as well. Solem and Olsen (1953) recommended the use of these drugs in icteric patients because of their effect in decreasing hepato-cellular jaundice as opposed to obstructive jaundice but Katz *et al.* (1957) showed that prednisone or corticotrophin reduced serum bilirubin values even in patients with extrahepatic obstructive jaundice. Urinary bilirubin excretion decreased simultaneously and, as there was no increase in fæcal bile or stercobilinogen, it appeared that the drugs delayed the breakdown of red cells or hæmoglobin rather than stimulating the excretion of bile by the liver.

Review of the literature shows that dramatic (50%) reduction in serum bilirubin levels within seven days of steroid or corticotrophin administration is frequent in patients with hepatitis, but relatively uncommon in extrahepatic obstructive jaundice. Its use therefore appears to have clinical application as a diagnostic test, despite its lack of biochemical specificity, and this is supported by recent experiences in 7 cases (Fig. 1) (Jones and Summerskill, 1958).

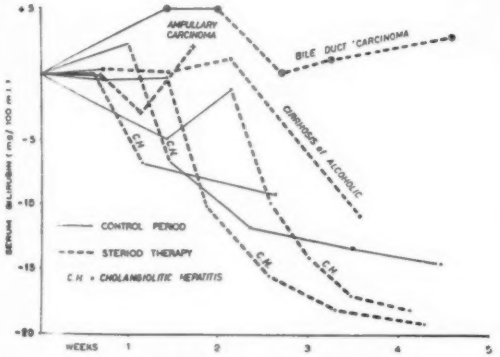



FIG. 1.—The effect of steroids on jaundice.

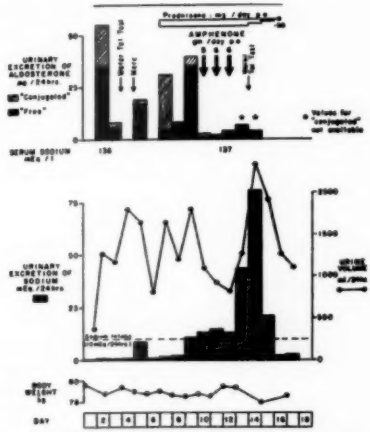



FIG. 2.—The effect of amphenone on urinary excretion of aldosterone and sodium in a patient with ascites.

In all patients the serum bilirubin level prior to treatment was above 12 mg./100 ml. and both clinical and biochemical evidence suggested obstruction. In 2 patients with extrahepatic obstruction, the response to steroid therapy was trivial and brief. A patient with cirrhosis showed no response for two weeks; then biochemical improvement, unrelated to clinical improvement, occurred. In contrast, 4 patients with "cholangiolitic" hepatitis showed an immediate response to steroid therapy. The fall in serum bilirubin levels progressed rapidly in 2 patients in whom treatment was continued, but biochemical improvement was slower after the drug was withdrawn in the other 2 patients. If, under such circumstances, treatment with steroids is continued, the less specific action of these drugs (improvement in appetite

and subjective well-being with decrease in jaundice not fully related to histological improvement in the liver) demands their cautious withdrawal during the apparent recovery phase in case relapses occur.

(3) *Ascites.*—The theoretical pathogenesis of ascites is compounded of several factors, but which are causal and which are secondary effects is not clear. Potentially the most important influence in maintaining the ascitic state is renal conservation of sodium and water. Of the hormones metabolized by the liver and capable of contributing to this mechanism, aldosterone, A.D.H. and possibly œstrogens deserve special consideration.

High levels of urinary aldosterone occur in patients with liver disease, especially in the presence of ascites, and the unconjugated portion of aldosterone is excessive, perhaps reflecting impaired hepatic function. A direct approach to the relationship between ascites and adrenal function by bilateral adrenalectomy has been utilized on individual patients by Marson (1954) and Giuseffi *et al.* (1957). Both patients had an immediate sodium diuresis after operation, but improvement in the ascites was much slower and symptoms of adrenal insufficiency followed, particularly sodium depletion in excess of that found in patients undergoing adrenalectomy for other diseases. Ascites re-accumulated unless careful control was exercised over dietary sodium and steroid maintenance. Mercurial diuretics, previously ineffective, secured an effective sodium diuresis after operation. Both patients finally lost their ascites but its tendency to re-accumulate shows that extra-adrenal factors are also important in the sodium and water retention of liver disease.

Summerskill and Crabbé (1957) used Amphenone, a drug which inhibits aldosterone secretion, in 4 patients with ascites complicating cirrhosis. In 2 patients whose ascites responded to bed rest, sodium restriction and mercurial diuretics, there was no increase in sodium excretion, despite the reduction of urinary aldosterone levels to the normal range. In contrast, 2 patients who were resistant to routine management had impressive sodium diuresis, urinary sodium levels rising from less than 1 mEq. to 60–80 mEq. in twenty-four hours. Urine aldosterone levels, previously abnormally high, fell to within the normal range when Amphenone was given (Fig. 2). In both these subjects impending hepatic coma occurred and disappeared when the drug was withdrawn. This and other toxic reactions constitute a great disadvantage to Amphenone therapy. The patients also received prednisone and in one patient a small sodium diuresis (<10 mEq. in twenty-four hours) occurred (Fig. 2), apparently in response to steroid therapy. Similar responses in patients with ascites have been reported (Muller *et al.*, 1956) but they are unusual and difficult to explain. There was no alteration in urinary aldosterone levels during prednisone therapy in these patients.

The terminal phase of ascites in the absence of other complications is one of progressive hypotension, oliguria, hyponatræmia and avid water retention. Although these symptoms suggest sodium depletion, the infusion of 200 ml. of 5% sodium chloride effected no clinical or biochemical improvement in 7 patients, which is in accord with the observations of others. The prognosis at this stage is very poor and it is uncertain whether hyperaldosteronism contributes significantly to the syndrome, although increased antidiuretic hormone activity could explain it.

Factors related to liver function, including low serum albumin levels and the impaired metabolism of aldosterone and other hormones, are probably important in all phases of ascites formation. Portal hypertension appears to influence the site of fluid collection as well as contributing to its accumulation. Hyperaldosteronism seems to be clinically related to the more advanced phase of resistance to diuretics, as adrenalectomy re-establishes sensitivity to diuretics with loss of the ascites. Nevertheless, as sodium and water can still accumulate under these circumstances, extra-adrenal factors, including neurohypophyseal function and increased œstrogen activity, have to be considered.

ACKNOWLEDGMENT.—I am grateful to the Editor of the *Lancet* for permission to reproduce Fig. 2.

## REFERENCES

BROWN, H. (1957) *Gastroenterology*, **33**, 258.
CHART, J. J., GORDON, E. S., HELMER, P., and LE SHER, M. (1956) *J. clin. Invest.*, **35**, 254.
GIUSEFFI, J., WERK, E. E., LARSON, P. V., SCHIFF, L., and ELLIOTT, D. W. (1957) *New Engl. J. Med.*, **257**, 796.
JONES, F. A., and SUMMERSKILL, W. H. J. (1958) Unpublished observations.
KATZ, R., DUCCI, H., and ALESSANDRI, H. (1957) *J. clin. Invest.*, **36**, 1370.
MARSON, F. G. W. (1954) *Lancet*, ii, 847.
MULLER, A. F., MANNING, E. L., and RIONDELL, A. M. (1956) *Schweiz. med. Wschr.*, **86**, 62.
PLAGER, J. E., TYLER, F. H., HECHT, H. H., and SAMUELS, L. T. (1954) *J. clin. Endocrin.*, **14**, 80.
SOLEM, J. H., and OLSEN, A. (1953) *Acta med. scand.*, **146**, 281.
SUMMERSKILL, W. H. J., and CRABBÉ, J. (1957) *Lancet*, ii, 1091.

# Clinical Section

President—E. W. RICHES, M.C., M.S., F.R.C.S.

[*February* 14, 1958]

MEETING AT THE MIDDLESEX HOSPITAL, LONDON

**Hypophysectomy for Incipient Blindness Due to Progressive Diabetic Retinopathy.**—J. D. H. SLATER, M.B., M.R.C.P. (for J. D. N. NABARRO, M.D., F.R.C.P.).

*History.*—Mr. N. H., aged 33, had had diabetes mellitus since the age of 9. From puberty, control of his diabetes had been difficult owing to his large and fluctuating insulin requirement (80–200 units daily, but reaching 350 units daily in 1943). Diabetic retinopathy was first recognized on routine examination in 1950. Since early 1956 his eyesight had been failing rapidly due to recurrent vitreous hæmorrhages. In the spring of 1957 he became blind in the right eye and until his operation was unable to read with the left eye. Mild proteinuria and mild neuropathy had been present since 1953.

*Pre-operatively* he required 64 units of soluble insulin in two doses with a diet containing 125 grams of carbohydrate. The blood pressure was 150/90 and his weight 12 st. 9 lb. Renal function studies showed a glomerular filtration rate (inulin clearance) of 108 ml. per minute, the blood urea was 29 mg./100 ml., and the urine deposit normal. The serum cholesterol was 310 mg./100 ml. Ophthalmoscopic examination revealed an extensive retinal detachment on the right and retinitis proliferans with retinal hæmorrhages on the left (Mr. Derek Ainslie).

*October* 1957: Hypophysectomy was carried out by Mr. Valentine Logue. This was technically difficult but appeared complete; Zenker's solution was used.

*February* 1958: His diabetes mellitus is well controlled with a reduced insulin dose (48 units soluble insulin daily) despite an extra 50 grams of carbohydrate daily. He feels well and is back at work as sales manager of a large concern. He takes cortisone 15 mg. daily, tri-iodothyronine 40 $\mu$g. daily and Pitressin Tannate 10 units i.m. every three to four days as replacement therapy. He is able to read small print with a magnifying glass although two further small vitreous hæmorrhages have occurred since his hypophysectomy. Complete removal of all functioning pituitary tissue is indicated by the development of myxœdema five and a half weeks post-operatively, the twenty-four-hour neck uptake of radio-active iodine falling from 26% to less than 4%.

**Dr. Nabarro:** Late complications affecting the blood vessels, kidneys and retina are becoming increasingly important in juvenile diabetics. Once retinitis proliferans has developed it usually progresses rapidly to total blindness and little can be done to prevent this disastrous complication. In 1953, Poulsen reported a patient in whom progressive diabetic retinitis had been arrested following the occurrence of pituitary necrosis. Luft and Olivecrona (Luft *et al.*, 1955) subsequently performed total hypophysectomy in a series of diabetics with severe retinitis and there seems to be little doubt that some patients were improved.

Three points require special emphasis. Hypophysectomy must be complete if lasting benefit is to be achieved; in contrast patients with widespread breast cancer may be greatly improved after partial or incomplete hypophysectomy. Post-operative complications are more common in diabetics than in cancer patients undergoing hypophysectomy; this is probably due to the arterial changes of long-standing diabetes. Thirdly, the management of the diabetes presents a number of special difficulties in the early post-operative period.

At the Middlesex Hospital 3 patients have had hypophysectomy performed for progressive diabetic retinitis. One died seven days after the operation. It is too early to claim that blindness has been prevented by the operation in the other 2, although there are signs that the retinitis is less active. The reason for showing this patient is to demonstrate that hypophysectomized young diabetics can be maintained in satisfactory health and are able to lead an active life.

REFERENCES

LUFT, R., OLIVECRONA, H., IKKOS, D., KORNERUP, T., and LJUNGGREN, H. (1955) *Brit. med. J.*, 1, 752.

POULSEN, J. E. (1953) *Diabetes*, **2**, 7.

**Sensory Nerve Conduction after Traction Lesion of the Brachial Plexus.**—GEORGE BONNEY, M.S., F.R.C.S., and R. W. GILLIATT, D.M., M.R.C.P.

Failure of recovery after a complete supraclavicular traction injury of the brachial plexus is often due to avulsion of nerve roots from the spinal cord. The lesion of the posterior roots is between the posterior root ganglion and the cord, and consequently the peripheral axons of this root do not undergo degeneration. Previous work (Bonney, 1954) has shown

that under these circumstances axon responses can be produced in the skin supplied by the affected nerve, long after the period required for axonal degeneration. The examination of these responses is a valuable guide to the placing of the lesion. In the present case it has been possible to provide additional proof of the integrity of the peripheral axons, by the demonstration of afferent impulses in the nerves of a limb paralysed by a traction lesion of the brachial plexus.

*Case History* (Patient referred by Mr. K. I. Nissen)

P. D. H., a man aged 24, was involved in a motor cycle accident on October 19, 1957, and sustained a traction lesion of the right brachial plexus. The initial examination showed complete flaccid paralysis of the muscles of the right arm and shoulder girdle with sparing of trapezius and rhomboids and partial sparing of serratus anterior. There was complete sensory loss over the dermatomes C.5 to T.1, with patchy sensory loss over the dermatomes C.3 and C.4. There was a right Horner's syndrome, and the skin of the right upper limb was dry. Screening showed normal diaphragmatic movements. The paralysis was unchanged in February 1958, by which time there was considerable wasting of the affected muscles.

*Investigations.*—Strength-duration curves (22.1.58) of representative muscles showed reaction of degeneration. Vasomotor responses (22.1.58): Resting skin temperature of digits of affected hand 24·5° C. No response to fifteen minutes' heating of the healthy hand and forearm. Electromyography (15.1.58): Right thenar muscles explored with needle electrode. Profuse fibrillation but no motor unit activity. Electrical stimulation of median nerve trunk at the wrist with brief shocks produced no electrical or clinical response from the thenar muscles.



FIG. 1.—Response to intradermal histamine on radial and ulnar sides of affected forearm.

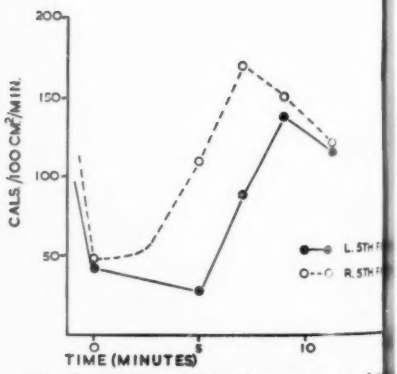



FIG. 2.—Cold vasodilatation response of fi fingers of healthy (left) and affected (right) ha compared.

*Axon responses* (25.11.57 and 22.1.58).—Response to intradermal injection of histamine was normal on the ulnar aspect of the forearm but on the radial aspect was that of axonal degeneration (Fig. 1). The cold vasodilatation response of the second and fifth digits was similar to that shown by these digits on the healthy side (Fig. 2).

*Demonstration of afferent impulses* (15.1.58).—The method of direct recording from sensory nerve trunks described by Gilliatt and Sears (1958) was used. Sensory action potentials were recorded without difficulty from the median and ulnar nerves at the wrist on both sides (Fig. 3). Stimulus intensities and the positions of stimulating and recording electrodes were the same in the two arms. Although the potentials on the affected side were slightly smaller in amplitude than those recorded from the opposite arm, their latency was not significantly increased.

*Discussion.*—In this case there was clinical evidence of a complete degenerative supraclavicular lesion of the brachial plexus. The sparing of the rhomboids and of part of

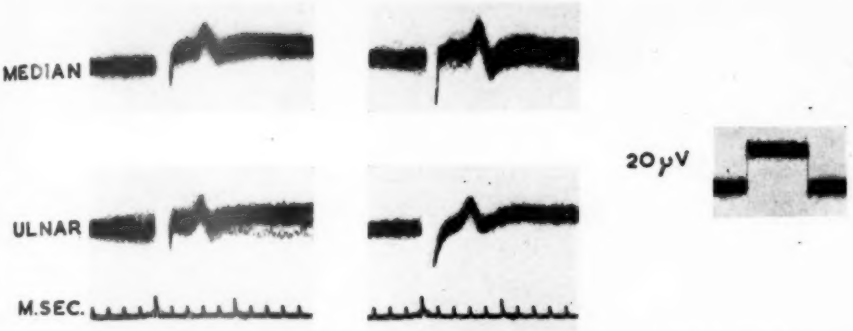



FIG. 3.—Records from median and ulnar nerves at the wrist during stimulation of index and little fingers respectively. Tracing shows stimulus artefact followed by nerve action potential. In each case twenty sweeps superimposed.

serratus anterior suggested that the lesion of the V cervical nerve was distal to the intervertebral foramen, but no further evidence as to the placing of the lesion was available from clinical examination or from the usual investigations. The finding of normal axon responses in the second and fifth digits and on the ulnar aspect of the forearm suggested that for the axons in the VII and VIII cervical and I thoracic nerves mediating these responses, the lesion was proximal to the posterior root ganglion. The demonstration of afferent volleys in the nerves of the affected arm showed that this was true also for the large fast-conducting axons in these nerves. These findings are of special interest in that they show almost normal electrical activity in nerves detached from the spinal cord. They are of some practical importance in assessing prognosis.

## REFERENCES

BONNEY, G. L. W. (1954) *Brain*, **77**, 588.
GILLIATT, R. W., and SEARS, T. A. (1958) *J. Neurol. Psychiat.* In the Press.

**Traumatic, Right-sided, Diaphragmatic Hernia: a Mistake in Diagnosis.**—J. K. ROSS, F.R.C.S., and L. P. Le QUESNE, D.M., F.R.C.S.

In August 1956 Mr. T. S., a taxi-driver, was admitted to the Middlesex Hospital for surgical treatment of a chronic duodenal ulcer. He gave a sixteen-year history of dyspepsia. Five years previously he had had a course of in-patient medical treatment with little benefit, and repeated barium meals had shown a distorted, deformed cap, though a crater had never been clearly demonstrated. X-rays of the chest before operation showed, as on previous occasions, opacity at the right base, reported as old basal pleurisy.

On 22.8.56 the abdomen was opened through a mid-line epigastric incision. The stomach and transverse colon were found stretched tightly across the posterior abdominal wall and could not be delivered. The stomach was traced to the right and the pyloric portion was found to pass, together with the hepatic flexure of the colon, behind the right lobe of the liver, up into the chest through a 3 in. hole in the diaphragm. Neither viscus could be withdrawn into the abdomen, which was accordingly closed.

On going into the patient's history again after this operation it was found that his symptoms began in 1941, whilst in hospital recovering from injuries received when his house was wrecked by a bomb. He himself was buried up to his clavicles in fallen masonry for seven hours, incurring fractures of his right leg and of his 4 lower right ribs. At first his indigestion was ascribed to "nerves", but later, following a barium meal, to a duodenal ulcer for which he was treated for fifteen years. Throughout this time his symptoms were continuous rather than intermittent. Though he complained of post-prandial pain, this tended to be in the lower right chest rather than epigastric and his predominant complaint was of repeated vomiting of small quantities after meals. Further, he stated that he had had no relief from his symptoms whilst in hospital on a strict ulcer regime.

A retrospective examination of his various X-rays revealed that the pyloric portion of the stomach and duodenal cap lay unduly high and that the deformity was really due to external distortion (Fig. 1). Further, it could be seen that the opacity at the right lung base contained a few gas shadows, obviously in displaced colon. Whilst he was recovering from the laparotomy a barium enema was performed and this clearly showed colon above the diaphragm in the right thorax (Fig. 2).

On 5.9.56 the right chest was opened through the bed of the 9th rib. The hepatic flexure



FIG. 1.



FIG. 2.

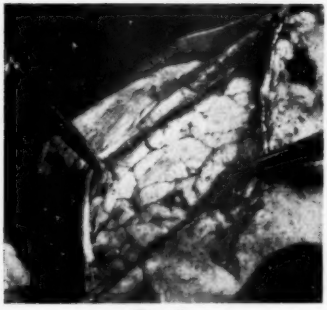


FIG. 3.

FIG. 1.—Barium meal film, showing the high, transverse position of the stomach, and the deformity of the pylorus and duodenum probably caused by external pressure from the margins of the diaphragmatic defect.

FIG. 2.—Barium enema film, showing the hepatic flexure of the colon lying in the right hemithorax.

FIG. 3.—Photograph showing the rent in the diaphragm. The hernia has been reduced and omentum can be seen through the defect. The lung is seen in the lower left corner of the picture.

of the colon, the pylorus, proximal duodenum and a mass of omentum were found lying free in the pleural cavity. They had passed through a split in the postero-lateral portion of the diaphragm and were lightly adherent to its margins. The split was oval in shape and had firm, fibrous edges (Fig. 3): postero-laterally it extended to within 2 in. of the costophrenic sulcus and antero-medially encroached on the central tendon. There was no duodenal ulcer. The viscera were returned to the abdomen, the defect closed with interrupted linen sutures and the chest closed. Recovery from this operation was uneventful.

Apart from its comparative rarity, the case is interesting because it demonstrates forcibly the great difficulty in reviewing a case afresh when once a diagnosis has been made, supported by a firm radiological report. Apart from the mode of onset, it is clear in retrospect that this man's symptoms were not typical of a duodenal ulcer; the absence of remissions and the failure of treatment to give relief were quite unlike the usual ulcer history. These features should have led to a questioning of the diagnosis, and probably would have done so had it not been for the repeated radiological reports of a duodenal ulcer. This patient's story clearly emphasizes yet again the importance of taking an accurate history and of questioning the results of ancillary methods of diagnosis if their results are at variance with the clinical picture.

The facts which distinguish the hernia in the case here presented from one of congenital origin are:

(1) The clear history of trauma.
(2) The absence of a hernial sac.
(3) The presence of adhesions at the margins of the defect.
(4) The fact that the aperture was not in the position of a recognized congenital defect.

Rupture of the right hemi-diaphragm due to closed injury with herniation of abdominal viscera into the right side of the chest is uncommon owing to the presence of the liver, which tends to plug, and therefore mask, small rents in the right diaphragm. The defect may only become apparent if the liver is ruptured and a right hæmothorax develops.

Closed injury can produce tears in the diaphragm in two ways. There may be a "burst" type of injury, the compressing force being transmitted to the stretched diaphragm by the upper abdominal viscera. This is said to be more common in the younger age groups, whose lower thoracic cage is more supple. Alternatively the diaphragm may be lacerated by fractured ribs and this would seem to be the mechanism involved in the present case.

Viscera which have been found displaced into the right side of the chest in reported cases include the liver and gall-bladder, transverse and ascending colon and cæcum, stomach, duodenum, omentum, small intestine and, in one instance, the pancreas. In the great majority of recorded cases the liver itself had become herniated into the chest, and in this respect the present case is of interest in that no part of the liver had passed through what was a relatively small defect.

**Renal Tuberculosis. Ileocystoplasty.**—E. W. RICHES, M.C., M.S., F.R.C.S.

Male aged 32.

*History.*—In 1947 he was invalided from the R.A.F. for a tuberculous pleural effusion. In February 1954 he had hæmaturia, increased frequency and pain in the right loin; acid-alcohol-fast bacilli were found in the urine. There was tuberculous cystitis and excretion and retrograde pyelograms showed an early tuberculous lesion of the right kidney (Fig. 1). Treatment with streptomycin (1 gram daily) and isoniazid (200 mg. daily) was started.

*Progress.*—His symptoms disappeared but in April 1955 the urine was again positive for tubercle bacilli. Domiciliary treatment was continued with PAS 12 grams daily and alternating three-monthly courses of streptomycin 1 gram twice weekly and isoniazid 100 mg. daily. By November 1956 he was symptom-free but the condition of the bladder had deteriorated and there was now more dilatation of the right lower calyx and some obstruction in the upper ureter (Fig. 2). The urine gave a positive culture for tubercle bacilli. By September 1957 he was micturating six times at night; the bladder held only 2 oz. (57 ml.). Excretion pyelography showed no excretion from the right kidney but hydro-ureter and hydronephrosis on the left (Fig. 3). There was reflux up the left ureter on cystography (Fig. 4): blood urea 39 mg. per 100 ml.

On October 11, 1957, ileocystoplasty was performed after the method of Yeates (1956) but with drastic resection of the rigid bladder dome. The left ureter was reimplanted over a polythene tube into the ileal graft; the thickened right ureter was divided and exteriorized pending right nephro-ureterectomy which was done six weeks later. The right kidney showed advanced renal tuberculosis with very little activity.



FIG. 1.—Retrograde pyelogram, February 1954, showing some dilatation of the right lower calyx and a little erosion. Left side normal.



FIG. 2.—Retrograde pyelogram, November 1956, showing narrowing of the right upper ureter and further dilatation of the lower calyx.



FIG. 3.—Excretion pyelogram, September 1957, showing left hydronephrosis and hydro-ureter with no excretion on the right.



FIG. 4.—Cystogram, October 1957. The bladder is contracted and there is reflux up the dilated left ureter.



FIG. 5.—Excretion pyelogram, February 1958. The function of the left kidney is good, and it has returned to normal size.

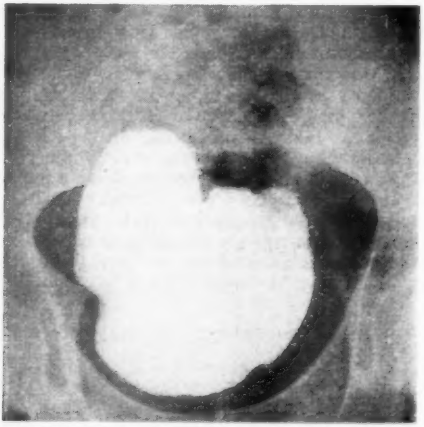


FIG. 6.—Cystogram. February 1958. The bladder held 20 oz. (568 ml.) without discomfort. There is no ureteric reflux.

*Result.*—In February 1958 he was much improved. He urinated only once per night, and he had been able to hold as much as 20 oz. He had gained 8 lb. in weight: blood urea 44 mg. per 100 ml. Excretion pyelography showed good function in the left kidney (Fig. 5) with minimal residual urine.

A cystogram showed a large bladder with no ureteric reflux (Fig. 6). No tubercle bacilli were found in the urine. Anti-tuberculous chemotherapy is being continued.

REFERENCE.—YEATES, W. K. (1956) *Brit. J. Urol.*, **28**, 410.

## BOOK REVIEWS

**The Eye in General Practice.** By C. R. S. Jackson, M.A., B.M., B.Ch.Oxon., D.O.M.S., F.R.C.S.Ed. (Pp. viii+152; illustrated. 21s. 0d.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

This is an excellent book and was recommended at the discussion at the General Practice Section Meeting at the Royal Society of Medicine on the subject of "Eyes in General Practice" in April 1957.

The book describes clearly how to examine the eye with a loupe and a focusing torch. The reviewer has often seen postgraduate students who have a good knowledge of the use of the ophthalmoscope and of the abnormal retinal conditions but who cannot examine the cornea or the iris.

The modern treatment of inflammatory conditions of the eye with corticosteroids (cortisone and hydrocortisone) demands a careful examination of the anterior segment of the eye to exclude iritis or iridocyclitis. This book is up to date because it clearly indicates under which conditions cortisone or hydrocortisone should be used. Not enough stress is laid, however, on the necessity for the use of cortisone or hydrocortisone in the treatment of iritis and iridocyclitis.

In the chapter on Choroiditis the author mentions that cortisone or other corticosteroids are now being used. Most ophthalmologists now agree that in cases of severe choroiditis systemic corticosteroids (cortisone, hydrocortisone, prednisone and prednisolone) are essential.

The chapter on squint and its treatment is good. The author advises that the squinting child should be treated with glasses, occlusion of the good eye, and orthoptics, before operative measures are resorted to. Reviews in various eye clinics have shown that operative treatment is best carried out at a very early age.

**Aortography. Its Application in Urological and Some Other Conditions.** By W. Barr Stirling, Ch.M., F.R.C.S.Ed., F.R.F.P.S.G. (Pp. vii+292; illustrated; 50s. 0d.) Edinburgh and London: Livingstone. 1957.

This monograph, based on the author's personal experience of some 500 aortograms, contains certain hitherto unpublished work and is a valuable contribution to both urology and radiology. The book is well assembled, the early chapters describing in detail the history, surgical anatomy, technique and potential hazards and complications of aortography. An interesting chapter is devoted to experimental work on pressure factors during injection of the dye.

In the author's hands aortography with modern contrast media is a comparatively safe procedure and his experience should help to reassure those urologists and surgeons who are still reluctant to use this diagnostic adjunct.

Mr. Stirling has devised a mechanical pressure injector which delivers 15 ml. of dye in less than one second and is connected electrically with the X-ray control table. At a time when retrograde catheterization of the aorta is gaining favour, he confidently advocates percutaneous puncture and finds his method simple, quick and free from serious hazard.

The second half of the book is devoted to the applications of aortography. Naturally most of the work is concerned with renal conditions. Some of the aortograms performed appear superfluous for not everyone will agree that aortography should be an essential investigation in all cases of congenital renal anomaly where surgery is contemplated.

There are useful sections on vesical neoplasm, disease in other abdominal viscera and bone tumour and the final chapter deals with intrinsic vascular disease giving a description of the technique of low aortography and of various aortic and peripheral vascular disorders. A striking feature is the very high quality of the abundant reproductions.

**Surgery: Principles and Practice.** Ed. by J. Garrott Allen, M.D., Henry N. Harkins, M.D., Ph.D., Carl A. Moyer, M.D., and Jonathan E. Rhoads, M.D., D.Sc.(Med.). (Pp. xxii+1495; illustrated; £5 10s. 0d.) London: Pitman. 1957.

This is the most exciting new textbook of surgery to appear since the war and presents a comprehensive and quite admirable exposition of the best in American surgical teaching at the present day.

The authors are well known to many people in this country and represent four widely separate university surgical centres in North America. Their average age is 45 and they bring

a freshness and enthusiasm to the task which makes the book a joy to read. They have co-opted a group of surgeons, each well known in his own particular field, and have then taken all these sections and welded them into what is a first-class introduction to general surgery. The book is new in every sense of the word and its foundations are physiology and pathology; these of course are the most solid foundations such a textbook could have, for it is from them that most new advances have come and it is also from them that a proper understanding of surgical practice arises.

It is unusual to find a textbook designed primarily for undergraduates with references at the end of each chapter, but these references are very well chosen, and if they do guide the student to start reading for himself in the original literature they will have been a worth-while innovation. Diseases of the endocrine system and the cardiovascular system occupy a very large part of the work whereas it is hard to find any kind of mention of amputations which, of course, will still need to be practised although they used to form far too large a part of the older textbooks. The illustrations are excellent. The photographs have only been included because they demonstrate something and the X-rays are well explained and for the most part extremely clear.

The printing and format of the book leave nothing to be desired; the double column pages are restful for reading and the type-face used is clear and attractive. It would surely be an advantage to bring this work out in future in two volumes since the present single one is much too bulky to hold comfortably and it is unlikely that the binding will long stand up to the wear which it should receive.

**Studies on Fertility.** Including papers read at the Conference of the Society for the Study of Fertility, London, 1956. Being Volume VIII of the Proceedings of the Society. Edited by R. G. Harrison, M.A., D.M. (Pp. x+138; illustrated; 25s.) Oxford: Blackwell Scientific Publications. 1957.

This excellent and carefully selected collection of thirteen papers, the eighth of such annual volumes to be produced, is largely devoted to male fertility problems. Current research on infertility rightly relies considerably on animal experiment, to which seven papers are devoted. The first paper by Mrs. C. Harvey on partitioned ejaculates emphasizes a finding of the utmost practical importance—the vastly increased sperm density in the first 0·5–1·0 ml. of semen ejaculated. In a later section, Mrs. M. C. N. Jackson rightly stresses the great advantages of using the split specimen technique of artificial insemination for cases of oligozoospermia. Hanley reports a technical triumph in epididymal surgery—the formation of spermatocele or cyst from which sperms were aspirated and inseminated with a resulting and successful pregnancy. There is an interesting paper from Liverpool on thermo-regulation of the testes emphasizing the effective radiator role of the scrotum.

One of the few sections on female infertility introduces a new long-acting progestational compound, 17-AHPC. It is highly potent and relatively free from side-effects. It is naturally vaunted for habitual abortion! Following a brief mention of low dosage pituitary irradiation the book ends appropriately with the effects of X-irradiation of the testes of mice. A stimulating and important book for the expert.

**Salmonellosis in Animals.** A Review. Review Series No. 5 of the Commonwealth Bureau of Animal Health. By A. Buxton, Ph.D., M.R.C.V.S. (Pp. vi+209; 25s. 0d.) Farnham Royal, Bucks: Commonwealth Agricultural Bureaux. 1957.

There was no up-to-date account of salmonella infection in animals and the author is to be congratulated on filling a much-wanted need. He has devoted a good many years to the study of salmonella organisms and is well qualified for the task.

The eight chapters of the book deal with: General Characters of the Salmonellæ; Classification; The Distribution of Salmonella Serotypes among Animals; Symptoms and Lesions of infection; Epidemiology; Immunology; Antibacterial Substances; and Public Health Aspects of Salmonella Infections. In addition there is a bibliography of over 1,500 selected references.

A great merit of this book is that the bacteriology and immunology are according to conventional teaching in the sense that they are based closely on the agreed systems used by the outstanding authorities in Denmark, Britain and the United States. It is impossible to write comprehensively about salmonella organisms without the use of tables and all the essential data are given in this form where possible. Among others is a most useful one covering several pages which shows the host species from which each salmonella serotype has been isolated. It includes the author references for each.

Even on a subject on which currently there is such a voluminous literature this book is unique in the cover it gives.

**Chronic Bronchitis, Emphysema and Cor Pulmonale.** By C. H. Stuart-Harris, M.D.Lond., F.R.C.P., and T. Hanley, M.D.Lond., M.R.C.P. (Pp. v+252; illustrated. 42s. 0d.) Bristol: John Wright & Sons Ltd. 1957.

This monograph, written as a record of the successive pieces of research carried out by the staff of the Department of Medicine of the University of Sheffield in the past ten years, deals successfully with the natural history and clinical patterns of bronchitis and is an invaluable guide to the family doctor who is overwhelmed with this type of case during the epidemic season. A valuable aspect of the work is found in the field studies on the epidemiology of this disease. The clinical picture, the problems in differential diagnosis, the significance of infection, emphysema and pulmonary heart disease, are all carefully considered.

Some contradictions occur with regard to the indications for antibiotic therapy. The presence of a purulent sputum is in one part of the book considered unreliable whereas elsewhere it is regarded as an index for modern antibiotic treatment.

Notwithstanding minor criticisms, the book is a model of its kind, admirably produced, and a worth-while addition to the ever-increasing literature on this subject.

**Medicine. Essentials for Practitioners and Students.** By G. E. Beaumont, M.A., D.M., F.R.C.P., D.P.H. 7th edition. (Pp. xviii+847; illustrated. 45s. 0d.) London: Churchill. 1958.

This well-known textbook of medicine, first published in 1932, has achieved the distinction of reaching its seventh edition this year. It has been translated into Italian and Spanish and is an invaluable compendium of medical practice. For the student, for whom it is primarily intended, it summarizes the essentials of medicine, eschewing all superfluous detail. It should also be extremely valuable to the family practitioner.

It is remarkable to find the whole of endocrinology and neurology, the cardiovascular, respiratory and alimentary systems, and tropical diseases, to name only a few, all succinctly summarized and the most recent advances touched upon—all from the pen of one man.

In this seventh volume the author has, however, permitted himself one departure from his normal practice: he has allowed a very good chapter on water and electrolytic balance to be contributed by his former registrar, Dr. P. H. Friedlander.

One or two minor criticisms should perhaps be made: it is questionable whether "disseminated" lupus erythematosus should be classified under "The Joints" for many other systems are, as Dr. Beaumont points out, involved. "Systemic" is, incidentally, a more accurate term than "disseminated". A special chapter on The Collagen Diseases would have been more in line with modern trends and polyarteritis nodosa, systemic lupus erythematosus, scleroderma and dermatomyositis could then have been integrated in such a chapter.

**Combined Textbook; Obstetrics and Gynæcology.** Edited by Dugald Baird, B.Sc., M.D., D.P.H., F.R.C.O.G. (Pp. xii+936; illustrated; 95s.) Edinburgh and London: Livingstone. 1957.

The 1957 edition of this popular textbook has been reduced in size from 1,411 to 936 pages and the editor hopes that the edition will be "more convenient to handle". Doubtless Professor J. M. Munro Kerr, who was responsible for the first four editions and who contributed to the fifth, will whole-heartedly approve. Much of the value lies in the excellent vital statistics which have been such a feature of Professor Baird's publications in recent years. Most sections are followed by references but it was disappointing that there was no reference to the work of Sutherland and Barnes on pelvic tuberculosis. The proof readers had failed to correct the dosages for streptomycin and PAS. It was surprising that in the section on heart disease Macrae's carefully documented publications are not mentioned, nor the classification of the American Heart Association. The Drew Smythe catheter was designed to preserve the forewaters and prevent intra-uterine sepsis—not prolapse of the cord. Air embolus occurs with an air insufflator (Fig. 438); only carbon dioxide should be used and only after biopsy and culture of the endometrium to exclude pelvic tuberculosis. In the operation of presacral neurectomy, a para-umbilical incision is an advantage and the ureters and left common iliac vein identified and thus avoided. In the chapter on antepartum hæmorrhage it is encouraging to read "that even in the absence of any history of hæmorrhage, routine ante-natal examination of the abdomen may reveal signs suggestive of placenta prævia".

The above are minor criticisms of an excellent textbook to which seventeen authors have contributed.

**The Pathology and Surgery of the Veins of the Lower Limb.** By Harold Dodd, Ch.M., F.R.C.S., and Frank B. Cockett, M.S., F.R.C.S. (Pp. ix+462; illustrated. 65s. net.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

The authors of this book have performed a great service in making the new knowledge on the venous system of the lower limb available in an easily assimilable form. The reader will be stimulated to review and to improve his approach to the surgical management of conditions which so greatly affect the "comfort and activity of mankind".

Operative treatment of varicose veins and ulcers is described with a clarity and wealth of detail from which not only the "young trainee surgeon" but his experienced elders as well cannot fail to improve their technique.

A notable feature of this book is the attention devoted to conservative treatment and post-operative management, for pre-eminently this is a field of surgery in which the operation is but an incident in the course of treatment.

For the treatment of varicose veins and venous ulcers much experience is needed to select the best method for the particular patient. The balanced sections on indications and contra-indications will restrain those junior surgeons, who inevitably lack this experience, from the temptation of performing all the operations on all the patients.

The illustrations are excellent.

**Operative Surgery.** Edited by Charles Rob, M.D., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. Volume 5. Orthopædic Surgery. (Pp. xiii+366+5; illustrated; £5 10s.) London: Butterworth. 1957.

This volume maintains the standard of the previous volumes already reviewed in these columns. It will probably prove most useful to the non-orthopædic surgeon when faced with the simpler types of operation such as for hallux valgus, hammer toe, in-growing toe nail, or removal of a semilunar cartilage. The more complicated operations are an imposing record of orthopædic skill and achievement.

**A Primer of Pædiatrics for the Senior Student and Family Doctor.** By E. Hinden, M.D.Camb., M.R.C.P.Lond. (Pp. xv+356; 25s.) London: Macdonald & Co. (Publishers) Ltd. 1957.

The author, in his preface, sets out the purpose of this book: "To deal with the common things the family doctor will encounter in his young patients, and to help him to manage them." The book is in three sections: (1) From conception to 4 weeks of age; (2) From 4 weeks to 2 years; (3) From 2 years to puberty. It is delightfully written and the author always ends each chapter by stating his own opinion based on current knowledge of the problem.

The opening chapter on "The Child's Heredity" is excellent and he goes so far as to define the "genes", so that the simple explanation of a defective gene leading to a dominant trait, and the defective recessive gene only giving rise to symptoms when it is present in both parents, is easily understood.

Section (2), from 4 weeks to 2 years, deals with normal growth during that period and then deals with the diseases of the various systems occurring in that period. The descriptions are full, adequate and stimulating. In Section (3), from 2 years to puberty, we have a full description of the virus diseases followed by the bacterial diseases and infestations. There is a good account of the School Health Service.

This book belongs to all those interested in the advancement of Pædiatrics. The writing flows from the first to the last page and the author constantly stimulates us with his original thought.

**Spastics in Cheyne Walk. An Account of the Centre for Spastic Children, Cheyne Walk, Chelsea.** Edited and compiled by Joan Saunders and Marjorie Napier on behalf of the Friends of the Centre. (Pp. xiv+156; illustrated. 20s.) London: Pitman Medical Publishing Co. Ltd. 1957.

This is an excellent book and the purpose of it is defined in the foreword by Admiral Godfrey, Chairman of the Chelsea Group of Hospitals. This book has been written to provide those who contemplate forming a centre for Spastics with information regarding the layout of such a centre, and the type of staff required to run it. This centre deals with the pre-school child as the local authorities have the responsibility of dealing with physical and mental incapacity when the child reaches school age.

We will look forward in due course to a detailed report on the cases treated at this centre over a period of years, showing the degree of improvement that has been obtained in their mental and physical conditions according to their original clinical grouping.

Any body of people contemplating setting up a centre for the treatment of spastic paralysis should read this book.

# Section of Comparative Medicine

President—J. B. BROOKSBY, D.Sc., Ph.D., M.R.C.V.S.

[*December* 18, 1957]

## SYMPOSIUM ON RECENT DEVELOPMENTS IN IMMUNIZATION AGAINST BACTERIAL DISEASE

## The Basis of Immunity to Anthrax

By H. SMITH, D.Sc., Ph.D., B.Sc.

*Microbiological Research Establishment, Porton, Wilts*

IN this précis, various preparations which immunize animals against anthrax will be described, and their relationship to the factors which appear to determine the virulence of *Bacillus anthracis*, will be discussed.

### NON-TOXIC IMMUNOGENIC PREPARATIONS FROM *B. anthracis*

Pasteur first vaccinated against anthrax using living attenuated cultures, and to-day live uncapsulated strains of *B. anthracis* (e.g. the "Sterne" strain) are still used for vaccinating bovines. The immunogenic products of the growth of *B. anthracis, in vivo*, were first demonstrated by Bail and Weil (1911) in the œdema fluid from infected animals. Watson *et al.* (1947) showed the immunogenic activity of such fluid was associated with the $\beta$ and $\gamma$ globulins and Smith and Gallop (1956) isolated from it an immunogenic, high molecular weight lipoprotein containing carbohydrate residues.

Attempts to produce a dead immunogenic preparation *in vitro* did not succeed until some thirty to forty years after the work of Bail and Weil. Gladstone (1946) finally produced an immunogenic culture filtrate in a serum medium. Later, an immunizing antigen was obtained in a synthetic medium, first by Wright *et al.* (1954), and then in greater yield by Belton and Strange (1954); it appeared to be a protein (Strange and Belton, 1954).

The preparations described above would actively protect guinea-pigs, rabbits and monkeys against anthrax but only appeared to have low-grade effect in mice; preliminary information from a trial being conducted at present on personnel from the goat hair industries of U.S.A. indicates that the immunizing antigen produced *in vitro* in a synthetic medium is effective in protecting man against anthrax (Brachman and Wright, 1958). In contrast to the immunogenic anthrax toxin described below, these various preparations neither produced œdema when injected intradermally nor were lethal when injected intravenously.

### THE VIRULENCE FACTORS OF *B. anthracis*

The virulence of *B. anthracis* is determined by the presence of at least two factors—an extracellular toxin and capsular polyglutamic acid (for a complete series of references *see* Smith and Keppie, 1955; and Smith, 1958). The anthrax toxin was first recognized in the blood of guinea-pigs dying of anthrax but later was produced *in vitro;* it is lethal when injected intravenously and produces an extensive area of œdema when injected intradermally. The toxin enhances the virulence of an attenuated strain of *B. anthracis*, inhibits the phagocytosis of *B. anthracis* by guinea-pig polymorphs, and inhibits the action of an anthracidal substance present in some normal sera and in extracts of leucocytes; it therefore acts as an aggressin in the early stages of anthrax. The toxin is a powerful immunizing antigen.

Capsular polyglutamic acid has been isolated from organisms grown *in vivo*. Like the toxin, it is an aggressin but it is non-lethal and does not evoke œdema. Furthermore, neither isolated polyglutamic acid nor that present in dead capsulated organisms is immunogenic.

### THE RELATIONSHIP OF NON-TOXIC IMMUNOGENIC PREPARATIONS TO THE TOXIN

Since the immunogenic toxin is produced by *B. anthracis, in vivo*, it appears to be the prime basis for immunity to anthrax. There is, however, a very strong connexion between this toxin and the two important non-toxic immunogenic preparations just described—the lipoprotein isolated from œdema fluid and the "*in vitro* antigen", i.e. the purified preparation (Strange and Belton, 1954) from culture *in vitro*.

Table I shows that there is a strong serological connexion between these two preparations and the anthrax toxin, because the latter is neutralized by sera prepared against the former. To follow the connexion farther, an important property of the anthrax toxin must be described. The toxin consists of two components; one (factor I) is deposited quickly during ultracentrifugation leaving the second (factor II) in the supernatant (Smith *et al.*, 1956). The

TABLE I.—SPECIFIC NEUTRALIZATION OF THE TOXIN OF *B. Anthracis*

| Toxin injected after mixing with ½ vol. of: | Œdema in guinea-pig (0·2 ml. i/d) | Lethality in mice i/v 1 ml. | 0·5 ml. |
|---|---|---|---|
| Saline .. .. .. .. .. | +++ | 25/25 | 23/25 |
| Normal horse serum .. .. .. | +++ | 10/10 | 11/15 |
| Horse antiserum (to spore vaccine) .. | Nil | 0/15 | 0/15 |
| Horse antiserum (to "*in vitro* antigen") | Nil | 0/10 | 0/15 |
| Guinea-pig antiserum (to lipoprotein) .. | Nil | 0/5 | — |

two components act synergically in tests for œdema production and lethality (*see* Table II). Stanley and Smith (1958) and Sargeant and Smith (1958) have purified factors I and II using the cellulose ion exchange columns of Peterson and Sober (1956). The most purified sample of factor I is a lipoprotein containing carbohydrate residues, and purified factor II is largely protein. Both factors very easily lose their potential toxicity even at 0° C. but retain their antigenic character.

There is little doubt that the non-toxic lipoprotein formerly isolated from œdema fluid was factor I of the anthrax toxin which had lost its potential toxicity in the separation procedure; indeed, experiments on active factor I showed that such procedures did destroy its potential toxicity.

The "*in vitro* antigen" appears to contain components connected with both factors of the anthrax toxin. This is indicated by two lines of evidence. Firstly, the "*in vitro* antigen" (*a*) will replace factor II in the synergic mixtures with factor I for œdema production or mouse lethality tests and (*b*) will replace to some extent factor I in the synergic mixtures with factor II for mouse lethality tests (*see* Table II). Secondly, the "*in vitro* antigen" contains two com-

TABLE II.—SYNERGIC MIXTURES OF FACTOR I WITH FACTOR II OF THE ANTHRAX TOXIN AND WITH THE "*in vitro* ANTIGEN"

| Material | Œdema production i/d, guinea-pig 0·2 | 0·1 | 0·05 ml. | Mouse lethality i/v 2 | 1 | 0·5 | 0·25 ml. |
|---|---|---|---|---|---|---|---|
| Factor I* alone .. .. | +++ | ++ | + | — | 0/5 | 0/5 | 0/5 |
| Factor II* alone .. .. | + | Trace | Nil | 6/25 | 1/25 | 0/25 | — |
| "*In vitro* antigen"* alone .. | Nil | Nil | Nil | 1/10 | 0/10 | 0/10 | — |
| *Mixtures* | | | | | | | |
| Factor I .. .. .. + Factor II .. .. .. | 0·05 ml. + 0·1 ml. | | +++ | | 0·25 ml. + 0·5 ml. | | 5/5 |
| Factor I .. .. .. + "*In vitro* antigen" .. .. | 0·05 ml. + 0·1 ml. | | +++ | | 0·25 ml. + 0·5 ml. | | 5/5 |
| Factor II .. .. .. + "*In vitro* antigen" .. .. | 0·1 ml. + 0·1 ml. | | + | 0·5 + 0·5 | 1·0 ml. + 1·0 ml. | | 2/5, 8/10 |

*13 ml. of original toxin produced 1·5 ml. factor I and 7 ml. factor II. The "*in vitro* antigen" of our colleagues Strange and Belton (1954) was made up at 0·1% w/v. All œdema production and lethality were specifically neutralizable by anthrax antiserum.

ponents which form common serological precipitation lines with factors I and II of the anthrax toxin in the standard procedure on Ouchterlony plates using anthrax antiserum prepared against the "*in vitro* antigen" (*see* Fig. 1) or against live spores. The relevant components

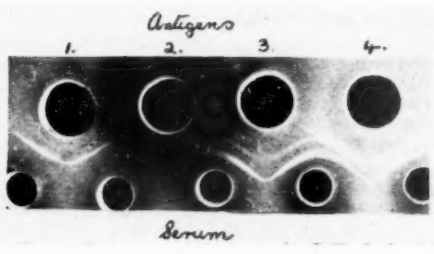



FIG. 1.—Serological precipitation lines on Ouchterlony plates. Antigen 1.—Purified factor I of anthrax toxin 0·3 mg. Antigen 2.—Crude anthrax toxin 8 mg. Antigen 3.—Purified factor II of anthrax toxin 2·6 mg. (this still contains approx. 2% of factor I). Antigen 4.—The "*in vitro* antigen" 0·3 mg. Serum.—anthrax antiserum prepared against the "*in vitro* antigen" (a similar picture is obtained using antiserum prepared against live spores). With different batches of toxin and different sera the line corresponding to factor I sometimes appears as a double line.

in the "*in vitro* antigen" are not exactly factors I and II of the anthrax toxin. Thus, apart from the obvious fact that the "*in vitro* antigen" is non-toxic, this antigen when it acts as factor II will only increase the œdema production of an amount of factor I which has a small inherent effect; it will not, as does authentic factor II, form an œdema-producing mixture with a smaller and separately unreactive amount of factor I. Furthermore, the "*in vitro* antigen" has no synergic effect on factor II as regards œdema production (*see* Table II).


## Summary

Of the two main virulence factors of *B. anthracis*—namely the toxin and capsular polyglutamic acid—the toxin is immunogenic and forms the prime basis for immunity to anthrax. The toxin consists of two factors which act synergically, and lose their toxicity very easily while retaining their antigenicity.

A non-toxic immunogenic vaccine prepared *in vitro*—an excellent practical vaccine—contains components which are closely connected with both factors of the anthrax toxin.


## References


Bail, O., and Weil, E. (1911) *Arch. Hyg. Biol.*, **73,** 218.

Belton, F. C., and Strange, R. E. (1954) *Brit. J. exp. Path.*, **35,** 144.

Brachman, P. S., and Wright, G. C. (1958) Personal communications.

Gladstone, G. P. (1946) *Brit. J. exp. Path.*, **27,** 394.

Peterson, F. A., and Sober, H. A. (1956) *J. Amer. chem. Soc.*, **78,** 751.

Sargeant, K., and Smith, H. (1958) *Biochem. J.* In preparation.

Smith, H. (1958) *Ann. Rev. Microbiol.*, **12.** In press.

——, and Gallop, R. C. (1956) *Brit. J. exp. Path.*, **37,** 144.

——, and Keppie, J. (1955) Mechanisms of Microbial Pathogenicity. Cambridge.

——, Tempest, D. W., Stanley, J. L., Harris-Smith, P. W., and Gallop, R. C. (1956) *Brit. J. exp. Path.*, **37,** 263.

Stanley, J. L., and Smith, H. (1958) *Biochem. J.* In preparation.

Strange, R. E., and Belton, F. C. (1954) *Brit. J. exp. Path.*, **35,** 153.

Watson, D. W., Cromartie, W. J., Bloom, W. L., Kegeles, G., and Heckly, R. J. (1947) *J. infect. Dis.*, **80,** 28.

Wright, G. C., Hedberg, M. A., and Slein, J. B. (1954) *J. Immunol.*, **72,** 263.


# Strain 19 and Other Brucella Vaccines


By E. C. Hulse, B.Sc., M.R.C.V.S.

*Ministry of Agriculture, Fisheries and Food, Central Veterinary Laboratory, Weybridge*


## Introduction

Prior to the introduction of S.19 vaccine to this country in 1941, a broth culture *Br. abortus* vaccine had been issued from Weybridge for many years. Under certain circumstances this vaccine was probably fairly efficient but its antigenic properties were unknown and it was rightly replaced by the S.19 vaccine.

Vaccination with S.19, an attenuated smooth strain (originally isolated by Cotton and Buck in 1923), had been started some years earlier in the United States and, by 1939, it had become firmly established there for the control of bovine brucellosis. The production of the liquid vaccine was begun at Weybridge with the assistance and advice of the United States Bureau of Animal Industry and output rapidly increased until an annual production of three-quarter million 5 ml. doses was attained. In 1944, the Ministry of Agriculture introduced the Calfhood Vaccination Scheme, whereby heifer calves from the age of 6 months to breeding age could be vaccinated at a small charge to the farmer by his own veterinary surgeon or by the staff of the Ministry. The scheme proved to be very successful and to-day over half of the vaccine issued is used for calfhood vaccination.

## Methods of Vaccine Preparation

In the preparation of the vaccine, care is taken to ensure that the smooth phase of the organism is always employed; the antigenicity of the vaccine is greatly reduced if dissociation is allowed to occur. For this reason the strain has always been cultivated on potato agar, although new techniques are now being evolved for production in a liquid medium; Roux flask culture is always laborious and the contamination risks are considerable. In 1956 the vaccine department at Weybridge moved into a new building equipped with the latest methods of ventilation for the production of a sterile atmosphere; the general improvements resulting from this have increased the yield by almost 20%.

Liquid culture techniques have been used by van Drimmelen (1956) at Onderstepoort for the production of S.19 vaccine. He has employed mechanical shaking of liquid cultures in large glass containers and, more recently (1957), the vortex system where 80 litres of liquid are revolved at 1,000 r.p.m. for seventy hours and a 2,000 to 6,000-fold increase in growth

obtained. At Weybridge plans are now well forward to introduce experimentally the continuous culture system employed at Porton. In this apparatus there is a periodic flow of fresh liquid medium into a container which is mechanically stirred and supplied with sterile air through a sparger; the vaccine concentrate is drawn off at intervals at the rate of about one litre per hour.

### Freeze-drying of S.19 Vaccine

Freeze-dried S.19 vaccine has been produced in recent years by commercial laboratories and others in several countries and in particular in the United States; the commercial undertakings have, quite understandably, not been prepared to divulge the medium used for the suspension of organisms prior to freeze-drying. Skimmed milk is most frequently used as the suspending medium but at Weybridge the re-suspending properties of this medium have not been satisfactory and the medium of Naylor and Smith (1946) (basically thiourea, dextrin and ascorbic acid) has been used instead. This medium has produced a satisfactory product which reconstitutes instantaneously; after freeze-drying the resultant viability is over 70% of the original count and the residual moisture is about 1%.

To facilitate handling of the vaccine in the field, freeze-drying in glass-sealed ampoules has been avoided and rubber-stoppered bottles have been employed. A butyl rubber mix has been found which appears to be relatively impenetrable under vacuum to water vapour. The vaccine is dried with the rubber stopper *in situ* in the mouth of the bottle and a special two-pronged stopper has been developed for this purpose; the stopper is pushed home under vacuum when the drying cycle is completed.

The recommended concentration of viable organisms in S.19 vaccine at issue is $60 \times 10^9$ and the minimal vaccinating dose is $25 \times 10^9$; at Weybridge it has been considered advisable to employ a greater concentration than this and the corresponding figures are $80 \times 10^9$ and $40 \times 10^9$ respectively.

The object of freeze-drying S.19 vaccine is to retain its viability for as long as possible after drying. The "life" of the liquid vaccine is three months at 4° C. and, to be of any practical value, the duration of viability of the freeze-dried vaccine must be greatly in excess of this. It has been shown that dried vaccine will retain an issue viable count for nearly two years in the cold store and there seems to be no reason why this period should not be considerably extended. Tests on the viability of the vaccine at room temperature have been carried out after storage in the cold store for twelve months and a satisfactory count has been obtained up to the fourth week at room temperature. Counts on the vaccine stored at room temperature immediately after freeze-drying have indicated that a vaccinating dose can still be obtained up to the twelfth week compared with a maximum of four weeks in the liquid vaccine held under similar conditions.

Tests are now being performed on the dried vaccine under transportation conditions. Samples of vaccine have been distributed to various offices of the Ministry in Scotland and the West of England and have been returned at regular intervals for testing. Vaccine stored in the cold in these offices has retained a vaccinating dose for six months, which is the present extent to which the tests have been applied. Similar tests on an extended scale are now in hand and the vaccine is submitted to conditions similar to those to which it would be subjected in veterinary practice; the examination of returned samples has given encouraging results.

In a limited field trial a small number of calves and adult cows were vaccinated with the freeze-dried vaccine suspended in Smith-Naylor medium; no abnormal reactions were observed. The agglutinin response, ranging in titre from 1/40 to 1/320, followed the normal pattern of the liquid vaccine and the local reactions at the inoculation sites were not noticeably more severe. The temporary drop in milk yield which generally accompanies the use of liquid vaccine was also similar.

To allow for the average 30% loss of viability of the vaccine during the freeze-drying process, more vaccine concentrate is required and the various liquid culture processes already referred to may be of value in mass production techniques. Consideration will have to be given to the problem of the removal of the spent culture from the bacterial mass prior to freeze-drying and its replacement with the suspending medium. Greater contamination risks in handling of the mass culture will be involved and there may be the added risk of loss in viability because it will not be possible to freeze the bacterial suspension so rapidly after harvesting and prior to freeze-drying.

### Application of the Vaccine in the Field

McDiarmid (1957) has reported the results of a large experiment at Compton involving approximately 500 cattle and extending over seven years. Young cattle were vaccinated in groups: once at 6 months; once at 18 months; twice at 6 and 12 months; and three times at 6, 12 and 18 months. Cattle from each of these groups and controls were challenged with virulent *Br. abortus*, some at the 1st pregnancy, some at the 2nd and so on up to and including

the 5th pregnancy. The immunity did not apparently diminish over the five pregnancies, irrespective of the method of vaccination employed. The triple vaccination gave a slightly better immunity than the single injection. Since, however, S.19 vaccine stimulates the production of agglutinins which cannot be distinguished from those resulting from natural infection, the single injection at 6 months of age is more desirable because the majority of animals vaccinated at that age return to the negative status by 18 months of age. The presence of agglutinins in the adult animal is disadvantageous for those who breed pedigree stock for sale or where it is desired to remove infected animals from a herd by blood testing. The use of a non-agglutinogenic vaccine is under investigation and this will presently be described.

The results of the Compton experiments show that one dose of S.19 vaccine at about 6 months of age will confer a satisfactory immunity against *Br. abortus* infection for at least five pregnancies.

## Adjuvant Vaccines

(*a*) *Br. abortus*.—In the early days of S.19 production a non-agglutinogenic strain produced by McEwen and known as 45/20 was also used, particularly in adult cattle. Unfortunately it was found to undergo mutation and its use was discontinued. Interest has been reawakened in this strain recently since McEwen and Samuel (1955) showed that a heat-killed adjuvant vaccine prepared from this strain successfully immunized guinea-pigs. McDiarmid and Sutherland (1957) have subsequently compared the efficacy in guinea-pigs of living, heat-killed and dead adjuvant vaccines prepared from strains 19 and 45/20. Vaccine prepared with S.45/20 by any of these methods produced no agglutinins. Dead organisms of both strains suspended in Ringer gave poor protection; S.19 vaccine, both living in Ringer and dead in adjuvant, produced a slightly better protection rate than strain 45/20. The 45/20 adjuvant vaccine was slightly more effective than that prepared from the living suspension in Ringer.

The results of this trial have encouraged the Compton workers to begin an extended experiment on similar lines in cattle of breeding age. McDiarmid is of the opinion that the 45/20 adjuvant vaccine might be used as an adjunct to the present method of vaccination against brucellosis in cattle. It is suggested that, if the use of S.19 vaccine were eventually limited to calves of 6 months of age, the non-agglutinogenic S.45/20 vaccine could well be used in those herds where it was thought advantageous to vaccinate older animals also.

(*b*) *Br. melitensis*.—A somewhat similar situation now obtains with regard to the vaccination of goats against *Br. melitensis*. Renoux and his co-workers (1957) in Tunis have experimented with attenuated and adjuvant vaccines and the latest results show that a formol-killed vaccine prepared from a virulent strain of *Br. melitensis* suspended in a non-absorbable adjuvant gives a satisfactory immunity in goats for about six months.

Elberg and Faunce (1957) have shown that good protection can be obtained in pregnant goats by the use of a living strain of *Br. melitensis* which is smooth and avirulent; this is derived from a non-dependent mutant isolated from a streptomycin-dependent population. Its disadvantage is that, like S.19, it stimulates the production of agglutinins.

Jones, Thomson and Alton (1958) at Weybridge have shown that an adjuvant vaccine derived from a killed rough culture of *Br. melitensis* produces the same immunity in guinea-pigs without producing agglutinins as a similar vaccine prepared from a smooth agglutinogenic strain. This work has now been carried a step farther by comparing the value of rough and smooth adjuvant vaccines in goats with the living smooth vaccine obtained from Elberg. The results have shown that there is not a significant difference between the three vaccines when challenged with graded doses of virulent *Br. melitensis*. The living vaccine of Elberg was most effective, however, in preventing a generalized infection with the larger doses of the virulent strain. Although this vaccine is agglutinogenic, it is anticipated that it will produce better immunity under field conditions than either of the dead vaccines. There is, therefore, a striking similarity between this vaccine and S.19 *abortus* vaccine in this respect.

## Conclusion

To summarize, the campaign to control and eliminate bovine contagious abortion by the use of S.19 vaccine in Great Britain has given and continues to give satisfactory results. Approximately half a million heifer calves are vaccinated annually under the Calfhood Scheme and this single injection gives, in well over 90% of cases, a satisfactory protection against infection for at least five pregnancies. The keeping qualities of the vaccine can be enhanced considerably by freeze-drying and it is anticipated that the vaccine will be issued as a freeze-dried product from Weybridge in the next few months. Work on mass liquid culture methods merits further investigation but vaccine derived from such a source might have to be subjected to a trial in cattle before one could be assured that it is entirely satisfactory as an immunizing agent.

Preliminary experiments on an adjuvant vaccine derived from the non-agglutinogenic strain 45/20 show considerable promise. The combination of these two vaccines with the

intensification of the use of S.19 vaccine in young animals should enable all stock to become immunized and such a procedure would go a long way to freeing this country completely from a disease which has occasioned such heavy losses in the past. Finally, the very serious problem in some other countries of *Br. melitensis* infection in goats and its transmission to man may eventually be resolved by the use of a vaccine on similar lines to the S.19 vaccination against *Br. abortus* infection in cattle.

REFERENCES

ELBERG, S. S., and FAUNCE, K. (1957) *J. Bact.*, **73**, 211.
JONES, L. M., THOMSON, P. D., and ALTON, G. G. (1958). In press.
MCDIARMID, A. (1957) *Vet. Rec.*, **69**, 877.
——, and SUTHERLAND, F. B. (1957) *Vet. Rec.*, **69**, 1067.
MCEWEN, A. D., and SAMUEL, I. MCA. (1955) *Vet. Rec.*, **67**, 546.
NAYLOR, H. B., and SMITH, P. A. (1946) *J. Bact.*, **52**, 565.
RENOUX, G., ALTON, G. G., and AMARASINGHE, A. (1957) *Arch. Inst. Pasteur, Tunis*, **34**, 3.
VAN DRIMMELEN, G. C. (1956) *Onderstepoort J. vet. Res.*, **27**, 205.
—— (1957) *Onderstepoort J. vet. Res.*, **28**. In press.

## Immunological Response to Freeze-dried BCG

By J. UNGAR, M.D.

*Glaxo Laboratories Ltd., Greenford*

VACCINATION with BCG has become established in many countries as an effective measure for the control of tuberculosis. There have been marked differences of opinion in this country as to the value of BCG vaccine, but the recent report of the Medical Research Council (1956) on vaccination of school leavers has shown it to have proved of value under certain conditions. A liquid vaccine was used in this trial—up to now the universally accepted form of BCG administration, except in Japan.

It has been realized that the liquid vaccine has certain disadvantages. First, the culture has to be closely watched for changes in antigenicity and virulence due to the continuous subculturing at ten- to fourteen-day intervals, and elaborate tests are necessary for this purpose. More important for the practical use of the vaccine are two other handicaps: it has only a limited life of about fourteen days and there is no direct evidence as to the antigenicity and safety of the vaccine when it is used. The vaccine consists of live bacteria and contains no antiseptics, so that slowly-growing contaminants would be difficult to detect by conventional sterility tests. The biological control of BCG is a long process. Apart from the safety tests, which include those for absence of virulence in the BCG, it is important to establish that the particular batch contains the required number of viable organisms. A much higher content is liable to produce untoward local reactions (ulcers, lymphadenitis); a low content may result in an unsatisfactory tuberculin conversion rate. Such variations in effect between batches of liquid vaccine have been noted.

It has been known that bacteria can be freeze-dried without affecting their biological characteristics, and it was obviously sensible to try to apply this technique to BCG, particularly in view of the considerable advances made in freeze-drying techniques as used in the preparation of antibiotics.

An effective freeze-dried BCG vaccine should have the following advantages over the liquid type: (*a*) *Stability*.—The vaccine would under suitable conditions be stable for at least one year and be available for use at any time during that period. (*b*) *Uniformity*.—The vaccine could be standardized in terms of viable bacteria, so avoiding undesirable variations between batches. (*c*) *Safety and potency*.—Each batch can be submitted to safety tests and to potency tests to establish its antigenicity before release.

### GLAXO FREEZE-DRIED BCG VACCINE

A freeze-dried vaccine should be prepared in such a manner that it reconstitutes on addition of fluid to a homogeneous suspension of cells with a minimum of clumping. The medium in which the bacteria are dried should be non-antigenic and not liable to cause any reaction. In the past vaccines have been prepared in serum, 50% glucose, 1% sucrose, various concentrations of lactose, &c., but most of these have disadvantages. After prolonged trials we have chosen as a suspending agent an aqueous solution of 8·3% of dextran with 7·5% glucose. The vaccine (Ungar *et al.*, 1956) is prepared from the same strain of BCG as that used in the M.R.C. trial; in our experience there is no essential difference in the strains of BCG used in various laboratories and freeze-dried vaccine can be prepared from any of them.

The strain is grown in a submerged culture in Sauton's medium, with addition of 1/4,000 w/v Triton "WR 1339", at a temperature of 37° C. for nine days. The growth is centrifuged and the deposit reconstituted in the dextran-glucose medium and standardized to a final con-

centration by opacity measurements in the Spekker photometer. The vaccine is filled into special moulded ampoules, then freeze-dried and sealed *in vacuo*. After preparation it is tested for its content of viable cells and on laboratory animals for safety and potency. These tests take about ten weeks: only after their conclusion are batches released for general distribution. The freeze-dried material is easily reconstituted for intradermal use by adding 1 ml. of either sterile water or physiological saline to the ampoule.

The viability count of the reconstituted freeze-dried vaccine is worth mentioning, because it is this property of the vaccine that it is particularly important to standardize. During the process of freeze-drying, depending on conditions, a proportion of the suspension survives; in our technique it is about one-tenth of the bacteria originally present. We found that a modification of O'Hea's method (1955) was the most suitable for our purpose; in this 0·02 ml. drops from a platinum dropping pipette are applied to the surface of the medium held in small bottles (7 ml. bijou bottles) filled with 10% blood agar medium. The vaccine is diluted in Sauton's medium, with 1/4,000 Triton added to inhibit aggregation, and tenfold dilutions from $10^{-3}$ to $10^{-6}$ are made in duplicate from each batch. The diluted solutions are incubated in six bottles of medium, and an average of twelve counts is taken. The method, as used in our laboratory, seems to give reproducible results, and we believe that it enables us to issue vaccines of a constant potency and with satisfactory keeping properties for at least twelve months when stored below 20° C.

## Biological Studies in Animals

One of the basic properties of the BCG vaccine is induction of tuberculin-sensitivity in the inoculated animal. The generally accepted view being that tuberculin allergy is a convenient index of acquired resistance, we have used the tuberculin conversion test to assess the quality of the vaccine. It has occasionally been stated that the freeze-dried vaccine is slower in inducing tuberculin allergy than is a freshly prepared fluid vaccine. We have found that the time of the appearance of the reaction to tuberculin, and the intensity of the reaction, depend on the number of viable organisms in the vaccinating dose (Table I). Similarly, the size of the

Table I.—Tuberculin Conversion in Guinea-pigs after Immunization with Vaccines of Different Viability

| Vaccine Batch No. | Viable cell count (per ml.) | Tuberculin test (time after vaccination) | Tuberculin reaction (mm. induration) twenty-four hours after 10 units PPD intradermally (average of six animals and range) |
|---|---|---|---|
| Freeze-dried 94b .. | $20{\cdot}8 \times 10^6$ | 20 days | 8·7 ( 7–12) |
| | | 28 days | 15·7 (14–18) |
| Freeze-dried 73 .. | $10{\cdot}0 \times 10^6$ | 20 days | 8·3 ( 6–11) |
| | | 28 days | 15·5 (14–16) |
| Freeze-dried 62 .. | $0{\cdot}7 \times 10^6$ | 20 days | 8·3 ( 6–10) |
| | | 28 days | 11·2 ( 7–13) |
| Freeze-dried 50 .. | $0{\cdot}1 \times 10^6$ | 20 days | 2·2 (0–7) |
| | | 28 days | 8·2 (7–11) |
| Freeze-dried 50 Heat killed | 0 | 20 days | 0 (0) |
| | | 28 days | 0 (0) |
| Danish liquid vaccine (1·97) | $26 \times 10^6$ | 20 days | 6·2 (0–9) |
| | | 28 days | 11·0 (9–13) |

Vaccination dose and route: 0·1 ml. injected intradermally. 0 indicates less than 2 mm.

Table II.—Relation Between Viable Cell Count of Vaccines and Size of Local Reaction at the Vaccination Site

| Batch No. | Viable-cell count | Extent of local lesion at vaccination site at 17 days after vaccination: G.-pig 1 | G.-pig 2 | G.-pig 3 | G.-pig 4 | G.-pig 5 | G.-pig 6 |
|---|---|---|---|---|---|---|---|
| 78 | $60{\cdot}0 \times 10^6$ | 4 | 4 | 4 | 3 | 4 | 3 |
| 94b | $20{\cdot}8 \times 10^6$ | 4 | 3 | 2 | 2 | 3 | 2 |
| 73 | $10{\cdot}0 \times 10^6$ | 2 | 2 | 3 | 2 | 2 | 2 |
| 62 | $0{\cdot}7 \times 10^6$ | 2 | 2 | 2 | 2 | 2 | 1 |
| 50 | $0{\cdot}1 \times 10^6$ | 0 | 0 | 1 | 1 | 1 | 1 |
| 50x | 0 Heat killed | 0 | 0 | 0 | 0 | 0 | 0 |

0 = No lesion. 1 = Small < 4 mm. lesion with small scab. 2 = Lesion 4–6 mm. diameter with firm 2–3 mm. scab. 3 = Lesion 7–10 mm. diameter with firm 5–6 mm. scab and some ulceration. 4 = Lesion > 10 mm. diameter with firm > 6 mm. scab, ulceration and deep necrosis.

vaccination papule after inoculating 0·1 ml. of the vaccine intracutaneously depends on the number of viable bacteria. Table II shows that the size of the local lesion was related to the viable cell content. By standardizing our vaccine to a required strength, we are able to issue biologically active vaccines and at the same time to avoid the danger of excessive local or regional (lymphadenitis) reactions, such as have occasionally occurred with liquid vaccines.

Protection tests in animals vaccinated with BCG are still in the experimental stage. No satisfactory answer can as yet be given from experiments on vaccinated guinea-pigs or mice subsequently challenged with virulent tubercle bacilli. An indirect method of assessing acquired resistance by measuring the radio-activity of disintegrated labelled mycobacteria in vaccinated and controlled animals is under investigation. This procedure might lead to a method for quantitative evaluation of the vaccine's efficacy.

## Biological Studies in Children

When we began our investigations we had no information on certain essential questions. They were:

(*a*) What should be the content of viable organisms in the vaccine to give a satisfactory tuberculin conversion without untoward reactions?

(*b*) Does the biological effect of the vaccine diminish with the time of its storage even though the viable count does not alter?

(*c*) Should the dose for babies be different from that for older children or adults?

(*d*) Is the vaccine suitable for different routes of administration?

It is a great pleasure to state that, thanks to the support and unceasing efforts of Professor W. Gaisford, Dr. M. Griffiths, Dr. J. Lorber, Dr. W. Hartston, Professor F. Heaf, and more recently of the M.R.C. Committee on Tuberculosis and particularly Drs. D. G. Evans and T. Osborne, we have been able to formulate the correct composition of the freeze-dried vaccine as an effective and safe antigen for intracutaneous vaccination.

Lorber and his team (1956), and Griffiths and Gaisford (1956) in their independent trials, have established that the freeze-dried vaccine is an effective antigen for young babies, as is the fluid Danish vaccine. They have also confirmed the considerable practical advantages of the dried over the liquid vaccine for use in clinics.

(*a*) The dried vaccine enabled us to answer the first basic question: what should be the content of the ampoule, how much should be injected into a baby to achieve the object? In the preliminary trials on 276 newborn babies, Lorber *et al.* (1956) had found that vaccines of low viability produce smaller lesions, less involvement of axillary lymph nodes and a slightly lower conversion (94%) than the liquid Danish vaccine. Shortly afterwards Griffiths and Gaisford (1956) reported their results with freeze-dried batches of different viabilities. They concluded that a satisfactory tuberculin conversion occurred after intradermal inoculation of 0·1 ml. of the vaccine, provided enough viable organisms were present. "With such a vaccine the rate and extent of development of allergy, the size of the local reaction and the response to tuberculin testing a year after vaccination were all comparable with the results produced by injection of 0·037 mg. of the Danish fresh vaccine."

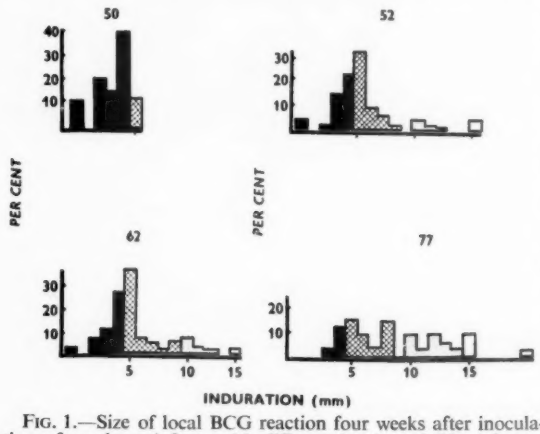



FIG. 1.—Size of local BCG reaction four weeks after inoculation of newborn infants with different batches of Glaxo freeze-dried BCG vaccine.

Fig. 1 shows that the size of the local lesion is directly related to the viable cell content of the vaccine used.

Batch 50 had a viable cell count of $0{\cdot}1 \times 10^6$ org./ml.
Batch 52 " " " " " " } $1{\cdot}2 \times 10^6$ org./ml.
Batch 62 " " " " " "
Batch 77 " " " " " " $10{\cdot}0 \times 10^6$ org./ml.

Fig. 2 shows the degree of Mantoux sensitivity to 100 TU four weeks after vaccination of newborn infants, and also demonstrates that the time of appearance of the allergy is proportional to the viable count.

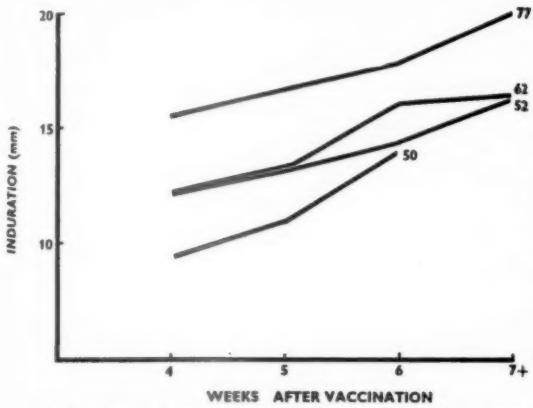



FIG. 2.—Rate of development of Mantoux sensitivity to 100 TU in newborn infants after injection of different batches of Glaxo freeze-dried BCG vaccine.

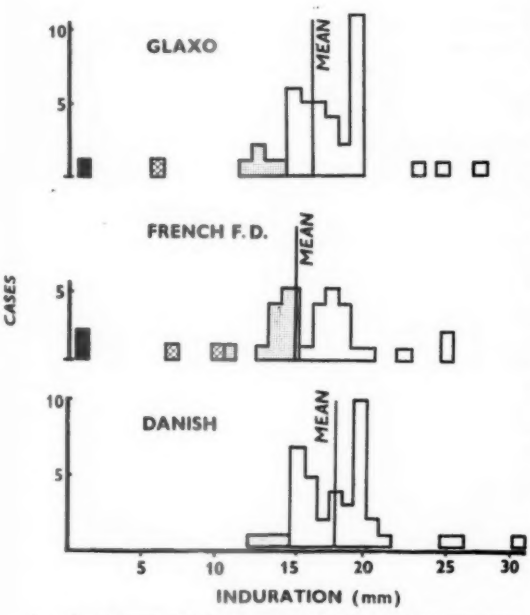



FIG. 3.—Degree of Mantoux sensitivity to 10 TU one year after vaccination of newborn infants with fresh Danish (0·075 mg.), Glaxo freeze-dried (Batches 52 and 62) and French freeze-dried vaccines.

Figs. 1, 2 and 3 are reproduced from Griffiths and Gaisford (1956) by kind permission of the Editor of the *British Medical Journal*.

The relationship between viable counts, size of local reaction to the inoculum and degree of Mantoux sensitivity is thus established. On subsequent trials it has been found that batches having viability counts equal to that of Batch 50 or lower, containing approximately 10,000–30,000 viable bacilli per inoculating dose, are unsatisfactory. On the other hand, batches of high viability, such as 77, containing 1 million organisms/dose, are more potent than the Danish liquid vaccine, but they tend to produce large lesions at the site of inoculation and regional lymphadenitis in a high proportion of babies. According to Griffiths and Gaisford, vaccines containing about 2–3 $\times$ $10^6$ viable cells are optimal; they produce nodules of fairly uniform size with little or no complication and a satisfactory lasting tuberculin conversion rate.

Similar conclusions to those of Griffiths and Gaisford were drawn by Lorber and coworkers (1957); Table III summarizes their results. When tested for tuberculin allergy with 10 TU four weeks after vaccination, babies inoculated with Batch 77 showed the highest conversion rate (86·8%).

The available results indicate that the tuberculin conversion after the freeze-dried vaccine is satisfactory. Fig. 3 compares the response to 10 TU tuberculin one year after vaccination with either the freeze-dried vaccine or liquid Danish vaccine. Lorber (1957) has retested 50 school children vaccinated a year previously with Batch 93a and found that all were tuberculin positive (jelly test or Heaf test).

It seems likely that tuberculin sensitivity produced by the dried vaccine will persist as long as that from the Danish vaccine, assuming that the size of the primary lesions reflects the extent of biological response to the antigen.

TABLE III.—VACCINATION LESIONS IN INFANTS AFTER BCG VACCINATIONS WITH BATCHES OF DIFFERING VIABILITIES

| Details | Batch of vaccine used | | | |
|---|---|---|---|---|
| | Freeze-dried Batch 50 | Freeze-dried Batch 77 | Freeze-dried Batch 93a | Danish liquid vaccine |
| Viable count .. .. | $0{\cdot}14 \times 10^6$/ml. | $23{\cdot}0 \times 10^6$/ml. | $11{\cdot}0 \times 10^6$/ml. | $5{\cdot}02 \times 10^6$/ml. |
| Number seen .. .. | 102 | 123 | 158 | 173 |
| Diameter of papules (mm.) Range | 1–15 | 2–28 | 2–28 | 3–18 |
| Diameter of papules (mm.) Average | 6·1 | 12·5 | 10·3 | 9·3 |
| Number of infants with papules of 20 mm. or more | 0 | 8 | 1 | 0 |
| Number of infants with papules of 15–19 mm. .. | 1 | 30 | 1 | 0 |
| % of infants with papules of 15 mm. or more .. .. | 0·9 | 30·9 | 15·8 | 6·3 |
| Number of infants with axillary lymph glands 5 mm. or more .. .. .. | 0 | 13 | 4 | 7 |

(From Lorber *et al.*, 1957.)

(*b*) In Lorber's series, vaccines were five to ten months old when vaccinations were begun. There was no evidence of deterioration, as judged either by the size of local reaction or by the extent of tuberculin response, in babies vaccinated with vaccines stored at room temperature throughout the four months' trial. Groups of infants vaccinated with it either at the beginning or at the end of the trial period gave the same response.

(*c*) The dried vaccine was standardized at the early stages with the primary object of using it for vaccinating babies. The first intimation that the same product might be suitable also for vaccinating school leavers came from Dr. W. Hartston, Tuberculosis Officer of the London County Council. In his preliminary trials Dr. Hartston compared Batch 62 with the Danish liquid vaccine and found that the responses after intradermal inoculation of either were similar. Since then, use of the freeze-dried vaccine has been extended to school leavers and reports from Dr. Hartston, Professor Heaf, Dr. Lorber and Dr. Griffiths and others have established that the original vaccine is also suitable for immunizing school leavers and contact cases in adults. This finding indicates that a single type of vaccine can be issued for general use.

(*d*) The intracutaneous vaccine is not the only type that has been available. My colleagues, Dr. P. W. Muggleton and Miss J. P. Farmer, have modified the freeze-dried technique to enable them to produce alternative types of freeze-dried vaccines suitable for oral use or for percutaneous administration by the multiple puncture method. The latter has been studied by Professor Heaf and by Dr. Hartston, whose experience seems to indicate that the multiple puncture method will give a satisfactory tuberculin conversion rate without causing any of the marked local lesions sometimes seen after intracutaneous inoculations.

There are many aspects of BCG vaccination still open to discussion and I can only briefly mention them. One is the question of the optimal age for vaccination. Pædiatricians would like to have vaccination begun before puberty. Occasionally doubts are expressed about the safety of the vaccine, but the reports of WHO on BCG mass imunization should convince any unbiased reader of its innocuousness. The opinion has recently been expressed that BCG has lost its value in communities with a high standard of living, because of the continuous decline of the tuberculosis mortality rate. This argument seems, however, to ignore the fact that the morbidity from the disease and the number of new cases of tuberculosis is still surprisingly high (report of the Medical Advisory Committee of the Research Foundation, 1957). It has to be admitted that the wider use of vaccination involves a reduction in the diagnostic value of the tuberculin test. Clinicians and epidemiologists will have to decide whether or not the extent of the protection afforded against tuberculosis makes this sacrifice worth while.

## REFERENCES


GRIFFITHS, M. I., and GAISFORD, W. (1956) *Brit. med. J.*, ii, 565.

LORBER, J. (1957) Personal communication.

——, FARMER, P., and MUGGLETON, P. W. (1957) *Tubercle*, **38**, 227.

——, HART, C. B. S., FARMER, P., and MUGGLETON, P. W. (1956) *Tubercle*, **37**, 187.

Medical Research Council (1956) *Brit. med. J.*, i, 413.

O'HEA, A. J. (1955) *J. path. Bact.*, **69**, 169.

Report by the Medical Advisory Committee of Research Foundation (1957) *J. Amer. med Ass.*, **164**, 951.

UNGAR, J., FARMER, P., and MUGGLETON, P. W. (1956) *Brit. med. J.*, ii, 568.

# Section of the History of Medicine

President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., C.B., M.A., D.M., F.R.C.P.

[*February* 5, 1958]

## Preventive and Curative Medicine in Ancient Peru [*Abridged*]

### PRESIDENT'S ADDRESS

By Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., C.B., M.A., D.M., F.R.C.P.

#### INTRODUCTION

IN choosing Preventive and Curative Medicine in Ancient Peru for my Presidential Address I have hoped to communicate to my readers some of the fascination that this subject has had for me, even before I went to that country. A great deal of work has been done to elucidate the ancient cultures of South America, including Peru, since Prescott's great book appeared just a hundred years ago, and the more that is found the more interesting and intriguing does the scene appear. The aspect of these civilizations to which I shall refer is not the least remarkable of their manifestations, and though the curative side of the picture can be more or less matched in other cultures, the preventive side, I venture to assert, was in many ways in advance not only of other contemporary civilizations, but of all throughout the world up to the end of the nineteenth century.

*The sources of our information.*—It is a well-known but very remarkable fact that the Indians of ancient Peru had no written language, though they had traditions handed down, in a carefully edited form, by minstrels, also a crude method of recording statistics, and possibly certain simple facts, by means of the *quipu* (which I will explain later); and finally, from the beginning of the fifteenth century, under the Inca Emperor Pachacutec, a series of paintings recording historical events—paintings which did not, unfortunately, survive the Spanish conquest. Consequently the sources of information available are limited to mummies (some, 2,000 years old), ceramics, embroideries, weapons, &c., found in the tombs and cemeteries and wonderfully preserved by the dryness of the climate; the accounts of the Spanish conquistadores, which must be accepted with caution owing to their strong prejudices against "heathen" practices and the reticence or even deliberate deception of the conquered peoples; and finally the contemporary customs and languages of the Indian tribes.

*The peoples.*—The origin of the peoples of South America is unknown, though Baudin [5] points out that "the excavations of Junius Bird . . . in Southern Patagonia have shown that man was hunting sloth, horse, and guanaco in that region between 6000 and 7000 B.C., so he must have been in Peru before that". The Incas were one of the many tribes inhabiting ancient Peru, and belonged to a group of tribes living in the neighbourhood of Cuzco and speaking the *Quechua* language.

The Inca empire lasted from about A.D. 1000 to the Spanish Conquest.

*Preventive medicine and public health.*—The Inca state was one of the most benevolent despotisms the world has ever seen, and certainly one of the most efficient. The State saw to it that every subject, whatever his age, ability or health, had sufficient housing, nourishment, clothing, and amusement (according to Tschudi [9] there were 158 fiestas during the year), security in marriage, freedom of worship, protection from special industrial hazards, freedom from debt (there was no money), security from oppression (the Inca sovereigns never abused their power or allowed others to do so), and protection from enemies outside. All these benefits were theirs, provided that they were never idle during working periods, stayed in their own provinces except when going up to the capital, Cuzco, for a feast, and did not break the laws. The Incas, in fact, gave their subjects a moral code far in advance of the peoples surrounding them, for as Baudin [5] remarks, "the chiefs of most of the surrounding tribes were bloodthirsty tyrants and gave a bad example. On the coast there was

sodomy; in the eastern woods and on the meseta itself cannibalism prevailed". Garcilaso [6], the historian of the conquest whose mother was an Inca princess, describes how a tribe, the Caranquis, rebelled against the Inca because they were not allowed to eat human flesh, killed the Peruvians and devoured them.

In the Inca state the most elaborate and accurate statistics were kept of births, marriages, and numbers of the population of different ages; in addition to statistics relating to crops, stores of grain, arms, &c. The instrument used to record such statistics was the famous *quipu* (or *quipo*), a cord from which hung numerous knotted strings of different colours, the position of the knots indicating units, tens, hundreds and thousands. Men were specially trained to make the quipus and to interpret them and they are believed to have recorded not merely statistics, but even historical events.

A census of the whole population of the empire was carried out every year, the population being divided into age groups. The accuracy of these statistics was safeguarded by severe sanctions, for the keeper of the records (called the *quipu-camayu*) who did not know what he should know, or who lied, was punished with death, "without hope of reprieve" [8] and the Indian who ran away to escape the census was poisoned. Special envoys of the Inca called the people together for numbering, even when they were in *articulo mortis*.

Though labour was compulsory, the sovereigns took care that it did not exceed the power of the individual, and for this purpose account was taken of age, sex, health and the nature of the work in question. Never were governors more careful of the health of their people; the mining of mercury, which gives rise to "tremors and nervous spasms", was forbidden (Garcilaso lib. 8); fishing for pearls was also prohibited; only a small number of Indians were sent to the coca plantations, situated in hot and unhealthy country, and these workers were invariably inhabitants of hot districts (the Spaniards by neglecting this precaution wiped out whole tribes [10]). For very laborious tasks there was a rota system, according to a law which Garcilaso (lib.5) calls the law of "alternative labour".

## Curative Medicine

*Anthropology*.—Now what did the peoples of ancient Peru look like? We can form a good idea from mummies, figures on ceramics, and the appearance of present-day people of pure Indian blood.

"The Incas were rather short and stocky, averaging about 5 ft. 3 in. in height, with broad shoulders, and the deep chest associated with a people who live in the rarefied atmosphere of the high Andes. They had a brown skin, straight hair, rather a broad face with a prominent nose, straight or slightly hooked, and little facial hair [11]." They were a muscular people. The modern Peruvian Indian, living at high altitudes, probably closely resembles the Incas. His blood picture reveals a tendency to macrocytosis with a moderate increase of the corpuscular volume and of the hæmoglobin content of the corpuscles, an increased proportion of reticulocytes and an increased activity of the hæmopoietic organs. Blood group O is predominant and Snyder and Coca-Deibert have suggested that the South American Indians are a pure race which separated from the main human trunk before factors A and B appeared.

*Sexual life*.—The principal goddess of fertility was called Imaimana, but it was Viracocha, the Creator, who had ordained that man should multiply and abound.

The phallic cult was preponderant and is well represented in ceramics. There were also idols, such as Isphana, who were prayed to as protectors of the urinary passages.

The onset of menstruation in girls was celebrated by a feast called *quicuchicu*, and during the first menstruation the initiates ate nothing but crude maize for the first two days. On the fourth day they cleansed themselves and put on a dress called the *angallo axo* and white woollen sandals.

The Peruvians, especially the upper classes, had a horror of incest and marriage was prohibited between a man and his daughter, sister, aunt or niece, the Inca himself being the only exception, for he always married his sister.

The local governors were presented with wives by the Inca from among the Virgins of the Sun.

Sexual perversions were common among some of the tribes (but not the Incas) including sodomy, bestiality and exhibitionism, sometimes practised in the temples of gods to whom these practices were supposed to be pleasing.

Garcilaso relates that when an Indian general, Auqui Titu, conquered some coastal valleys in which he found sodomy being practised, the Emperor commanded that not only the actual offenders but also all initiates should be burnt alive in the public square, and that the trees on their land should be burnt down and the roots torn up, so that no memory of them should survive.

In the Inca state adultery and fornication were punishable with death.

*Artificial deformations.*—The practice of producing artificial deformities of different parts of the body seems to have prevailed in Peru from time immemorial and such deformations are well represented in ceramics.

The perforation of the nasal septum for the insertion of a *nariguera*, or disc with a ring top for attachment, was a common practice among the ruling caste. The name *paychi* seems to have been attached indifferently to this operation and to the corresponding perforation of the ears for the insertion of discs of increasing size. Though the wearing of both kinds of discs was a sign of caste, the perforation of the ear lobes had a special significance, and was, perhaps, a blood-rite, analogous to Jewish circumcision [12]. *Chicha*, an alcoholic beverage made from maize was used as an anæsthetic for this operation [13].

Deformation of the skull was also a common practice, the object and mechanism of which are still much debated. Lastres [11] describes two main types of deformation, the first, shown by skulls exhumed in the region of Tiahuanaco and around Lake Titicaca, he calls "la deformación echada", or flattened deformation, in which the frontal bone is flattened almost horizontally, forming a plane with the parietals and resulting in an antero-posterior elongation. The second type described by Lastres is called by him "levantada" or elevated, and is found in the coastal regions, especially in the tombs at Ancón. In this deformity the frontal bone is pushed upwards, as are also the parietals, by antero-posterior compression by means of a clamp-like apparatus called a *chuco*. Several other varieties of cranial deformation are also encountered. The object of this practice has been variously given as æsthetic, for the subjugation of conquered peoples, as a religious rite like circumcision, as a caste distinction, to frighten enemies, &c., but nothing is certain here. The *chuco* was apparently applied soon after birth and continued until the child was about three years of age, after which the skull grew in the required shape without further persuasion.

*The doctors.*—As with all primitive peoples the medical conceptions of the ancient Peruvians were based on their religious beliefs and their main object in life was to conciliate the supernatural forces surrounding them, asking some to spare them, others to aid them [1]. The perpetual state of fear in which they lived was, in fact, at times responsible for pathological changes. Every illness was, in their conception, the result of some fault committed either by the patient himself or his neighbours and the best way to discover the cause of the malady was to make a sort of confession to the priest-doctor, whose job it was to elucidate what had gone wrong.

It was, then, by means of magic that the cause of the malady was discovered and the means for its cure selected.

The persons who treated the sick were a combination of priest, magician and doctor, and were attached to some *huaca*, i.e. a place held sacred, either because of some important event which had occurred there, or because it was dear to some divinity, or was a place of burial. These priest-magician-doctors, known as *hampi-camayoc* (the Spaniards called them *brujos* or *hechiceros*, i.e. sorcerers) were very numerous. Fig. 1 shows one of them driving



FIG. 1.—Magic cure (after Tello). [Copyright.]

out the demon of a disease. Their functions were to offer sacrifices and offerings, to hear confessions, to give advice, and to heal by driving out the demon causing the disease, and finally to avert plagues and pestilences. Many people regard them as akin to *shamans*. These men or women were chosen in the first place from among those who were regarded as

set apart, e.g. those who had been born in the fields in a thunderstorm (called *chuqui-illa*), o those who were said to have been "born of the lightning", or "sons of the lightning", o twins or triplets. Other priests, known as *ccamascas* or *mascas* [2, 3], attributed thei powers to the thunder, the idea being that thunder had occurred close to them producing an internal commotion during which they were endued with power to heal with remedies o to answer questions put to them.

The persons who aspired to be priests or magicians went through a rigorous novitiate with fasting, bleeding, and a vegetarian diet consisting of herbs and maize. It was only after many months of painful abstinence that they were declared priests. During his novitiate the priest was called a *huamac*, but afterwards there was much specialization with consequent multiplication of names. The real doctor or *hampi-camayoc* was under an obligation to treat the Inca and his family and may even have been a member of the nobility himself.

Below him came the *ccamascas* or *soncoyoc*, who practised among the common people. There were many other grades, but there is a good deal of confusion in the use of their appellations by the old Spanish historians.

*Diseases.*—The sources of our knowledge of the diseases of ancient Peru are the examination of mummies by inspection, X-rays, &c., the representations in ceramics, and the accounts of the Spanish chroniclers, but the latter are, of course, confused by the imperfect diagnosis of the sixteenth century. Thus the devastating epidemic of about 1524, which killed the aunt, brother and sister of the Inca Huayna Capac whilst he was in the island of Puná and killed the emperor himself at Quito on his way back to Cuzco, was thought by Cieza de León to be small-pox, and Lastres agrees, but Pachacuti was inclined to call it measles; in any case it was an infectious febrile illness with a papular rash and a high mortality. Some have thought that it was *verruga peruviana*, a peculiarly loathsome disease which has been common in Peru for many centuries. It is characterized by fever, anæmia and a widespread nodular eruption of the skin, and Zarate [18] says that this disease was more destructive than small-pox.

Clear evidence exists of rheumatic disease and Williams [14] found signs of vertebral osteoarthritis, probably of rheumatic origin, in a Peruvian mummy. Rheumatism was probably very common, the humidity of the climate in some of the agricultural and mining districts being favourable to it [12].

Malaria was undoubtedly common on the coast and in the coastal valleys and was called *chucchu;* whilst as for cancer the only certain evidence is given by the very rare examples of what was apparently osteosarcoma.

There is no doubt that epidemics were fairly frequent and often led to the abandonment of the towns in which they occurred, which were thereafter regarded with superstitious horror. This may well be the origin of the "lost cities" such as Machu Picchu.

Typhus must have been common. It had, apparently, always been endemic in the sierra and from time to time caused serious epidemics, especially in the rainy regions [12].

Warts have always occurred in the same regions, especially in the ravines, and were called *sirki*.

Respiratory diseases were ill-understood, but nasal catarrh, cough, and pneumonia were certainly known and pulmonary tuberculosis was probably not uncommon; its spread being favoured by the system of *mitimaes*, under which populations of doubtful loyalty were transplanted from their native places to other parts of the country.

Tuberculosis of the bones is well represented in ceramics in the form of Pott's disease of the spine.

Tetanus infection appears to have been frequent, especially in children, and was called by the Spaniards the "three-day illness".

The possible incidence of rabies has been hotly debated. It probably occurred sporadically.

Coming now to endocrine diseases, goitre has been the subject of much study and was described by Bartolomé de la Vega, Calancha, Cobo and other authors as being common in some districts, such as Cuzco.

Acromegaly and achondroplasia are represented in ceramics. The existence of true dwarfism and gigantism rests chiefly on legend.

Artificial eunuchs were made by some of the tribes in pre-Inca times and according to Blas Valera the confessors in the Inca temples were either eunuchs or had sworn perpetual chastity.

Obesity is well represented in ceramics, and myxœdema is suggested by the descriptions of some of the Spanish chroniclers.

Of neurologic affections, deafness and deaf-mutism can be identified. Club foot, probably the result of an adult hemiplegia, is also represented, as well as facial paralysis and hare-lip (Fig. 2 (1) and (2)).




FIG. 2.—(1) Facial paralysis. (2) Hare-lip. (3) Multiple amputations. (4) Pruriginous skin condition. [Copyright.]

Eye troubles were common, such as gonococcal conjunctivitis, keratitis and perhaps trachoma. There are suggestions, too, of blepharitis, infectious panophthalmia, and tumours of the eye. Blindness appears to have been common but may sometimes have been inflicted in punishment. Epilepsy appears to have been commoner on the coast (among the Yungas and Mochicas) than in the mountains.

A curious complaint, called by the quechua Indians *taqui oncco*, or the dancing disease, has been described by Ondegardo and others and may be similar to the *tarrentism* of the Middle Ages in Europe, as it was cured by communal dancing.

There is good reason to believe that the use of coca, which was and is common among the Peruvian Indians, was not so harmless as some have maintained. Gutiérrez-Noriega [15] has found in such cases psychical and sensorial changes, modifications of visual and auditory acuity, auditory and visual hallucinations and alterations in time perception. In cases of serious intoxication there occur fantastic visionary effects, such as macroscopia, microscopia, distortion of image, and alterations of spatial perception, also thought changes such as acceleration of mental processes and obsessions.

The Peruvian Indians were not naturally a very cleanly people and it is not surprising, therefore, that skin diseases were common. Washing was, however, linked with their religious beliefs and the efficacy of water for cleansing from disgrace and sin was universally believed.

The *jigger* was a common pest, from which they protected themselves by wearing woollen sandals, or *uxuta*, whilst plasters made of the leaves of the *apichu* were used for killing this insect.

Ringworm and eczema appear to have been frequent and a pruriginous affection of the skin is shown in Fig. 2 (4).

Leishmaniasis, or *uta*, is endemic, especially in the foothills of the Andes. Lavoreria identifies this with the so-called "disease of the Andes" which attacked the Indians who went to cultivate coca under the Incas. Its corrosive action is noted and it is represented in

ceramics destroying the skin and producing facial disfigurement with destruction of the nose and lips.

The existence of leprosy in Peru is uncertain.

Pellagra may well have occurred in view of the almost exclusively maize diet of many of the tribes.

Genito-urinary affections: Cobo mentions retention of urine and the presence of gravel or stones in the bladder, but this appears to have been rare, perhaps because of the diuretic and calculus-dissolving action of chicha, the alcoholic beverage made from maize which is still so popular.

As regards the possible occurrence of syphilis Lastres devotes a whole chapter of his book to a discussion of the pros and cons. Whether syphilis was imported into Europe from Hispaniola by Columbus' returning sailors, or whether it existed in Europe and the Near East from ancient times, has been hotly debated on many occasions (sometimes in this Society) but I have no time to examine the evidence. It should be noted, however, that some of the Spanish chroniclers, writing soon after the conquest, stoutly defended the Peruvians from this charge.

Many skulls and long bones have been found in ancient Peruvian cemeteries with pathological appearances suggestive of syphilis, but the skull found by Tello and Williams [16] in Paracas in 1929 probably affords the most convincing evidence of the pre-Columbian existence of syphilis in Peru, and the word *huanthi*, in the quechua and amara languages, the most ancient of all the Peruvian languages, is believed to represent this disease.

Enteritis and dysentery were common, which is not surprising in view of their primitive hygiene and their consumption of raw vegetables.

Other bony lesions found, apart from those due to tuberculosis and syphilis, include exostoses, periostitis, necrosis and perhaps osteomyelitis. Moodie has described a tumour of the dura mater of the meningioma type.

## Surgical Treatment

Surgery was a very necessary art for such warlike peoples as the ancient Peruvians and Moodie says that no other race produced better surgeons, judging by the success of their operations. These surgeons were called *sirkaks*, and were probably distinct from the physicians. Their principal instrument was the *tumi*, of which many variants have been found, a crescentic knife usually of bronze and extremely sharp, with which the soft tissues were easily divided, though it may also have been used for trephining. Knives and plates of obsidian and of flint were also found by Tello in the necropolis at Paracas, as well as dressings of cotton-wool and of cotton thread, moulded to the shape of the original wound. As clips to hold the wound edges together the Indians employed the mandibles of a certain species of ant.

There has been a great deal of discussion as to the anæsthetic, if any, used at operations, but it seems clear from the testimony of Betanzos [13], supported by Tschudi's linguistic studies, that a stupefacient frequently employed, not merely for major surgical operations but also for ear piercing, was a special brew of chicha in which was infused the stalk of a fruit shaped like an almond and called by the Spaniards *espingo*. This drink was called *sora*.

Mutilations, including amputations of feet, hands, nose, and lips are frequently represented in ceramics and are often multiple (as in Fig. 2 (3)). Their origin and purpose are, however, still uncertain. Apart from those which might be due to leishmaniasis, leprosy, &c., there are many which seem to be artificial and were probably punishments for legal offences.

Fractures and dislocations were often attributed to the violence of a spirit inhabiting the body and were therefore treated by sacrifices and offerings on the spot where the trauma occurred, but more effective was the setting of fractures, with a paste containing coca, salt and white of egg which set hard and acted as a splint [12]. Operations performed included enucleation of the eye, reduction of large hernias, and castration [17].

A pre-Inca skull in the museum at San Diego, California, has fastened to it an apparatus in perfect condition, which appears to have been devised for controlling bleeding from the scalp. The portion of this apparatus passing over the vertex is wrapped in cotton-wool covered with gauze, stained in places with what appears to be blood. Most remarkable of all, the cotton-wool is soft and white and the gauze of finer texture than is made to-day. This was more than 1,000 years ago.

Suction and massage were used for surgical treatment and the *hechiceros* said they sucked the wounds so as to suck out blood and with it the disease [4]. This treatment was effective for reducing hæmatomata, extracting foreign bodies, arrows, and fragments of bone, and for relieving pain. The Indians believed that all inflammation was due to a foreign body, either visible or invisible.

Trephining in ancient Peru has received a great deal of attention and I have space only to give a brief outline of our knowledge of this subject. I have already referred to the *tumi*, the knife used for trephining as well as other operations. Fig. 3 shows a *tumi* bearing on

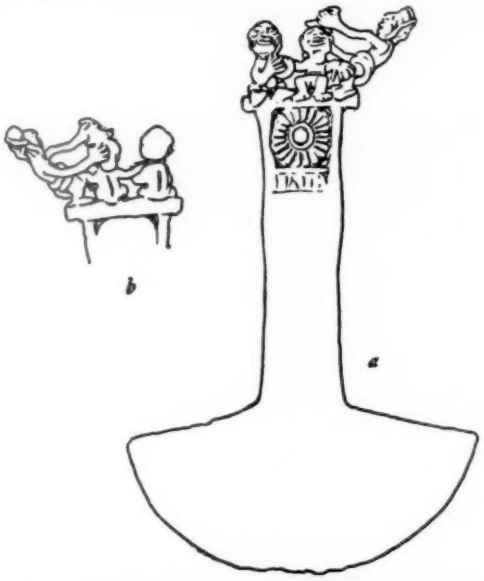



FIG. 3.—Tumi, bearing on the handle a representation of a trephining operation (after Antze). [Copyright. Reproduced by kind permission of the Director of the Museum für Völkerkunde, Hamburg.]

the handle a representation of a trephining operation, giving a very good idea of how this instrument was used. This *tumi* is of metal, but *tumis* of stone and obsidian were also employed in some early cultures.

There is much difference of opinion as to the object of this operation, but owing to the frequency of skull injuries among these warlike peoples symptoms such as epilepsy, due to compression or irritation of the brain, must have been common and were probably attributed to the presence in the skull of a restless spirit wishing to escape. Thus trephining might be expected to be used in such cases, as well as for symptoms due to other forms of compression or cranial disturbance, such as tumours of the brain or its membranes.

Many different methods appear to have been employed. A *tumi* with a crescentic edge would seem to be quite unsuited to cutting through the bone of the skull [19], without fatal results, and it was therefore probably used only for dividing the soft tissues, and when Callo and Quevado [20] carried out their astonishingly successful trephining with ancient Peruvian instruments in the hospital of Belén in 1944 they had to abandon the *tumi* when they came to bone and proceed using knives of obsidian and flint. Other methods seem to have included scraping with flint, obsidian, quartz or instruments of copper or bronze. The incisions in the skull were in the form of a square, a triangle, an oval, &c. Trephining by drilling was also employed, and one skull has a gold prosthesis inserted after a frontal trephining.

Neolithic trephining seems to have been rather haphazard and must often have been fatal, but the careful avoidance of the longitudinal sinus in two skulls testifies to a better anatomical knowledge and skill at a later date. Perhaps the most remarkable feature of the whole thing is the number of cases, as shown by the smoothed edges of the holes, in which the patient survived, not merely a single trephining but as many as three! Patients who survived trephining were apparently regarded as specially endowed with supernatural powers.

## OBSTETRICS

Childbirth, according to Garcilaso, seems usually to have been easy for the Peruvian Indians, for he says that directly afterwards, having washed themselves and the

babies in cold water, they returned to their housework as if nothing had happened. But there can be no doubt that they regarded it with respect and even fear. The earth was thought to be the special protector of women in childbirth and they sacrificed to it [10]. They burnt clothes to it, buried ewes alive, sacrificed maidens, and with the hearts of ewes they sprinkled blood to the Sun. Confession and purification were practised by the pregnant woman and in many of the tribes, including the Incas, the husband did so too and also fasted when his wife was at term.

The arrangements for the delivery are well shown in Fig. 4. The woman is seated naked



FIG. 4.—Childbirth. [Copyright.]

[Figs. 1, 2 and 4 are reproduced by kind permission of Professor J. B. Lastres.]

and legs apart on a low stool, or perhaps a filled sack, supported behind by her husband with his arms locked round her and attended to in front by the midwife.

The practice of abortion was common in pre-Inca times, but the Emperor Pachacutec forbade it under heavy penalty. Once again the Incas showed their enlightenment. In contrast the Arma tribe, who were cannibals, used to take women at about term, slit up their abdomens with great skill and speed, using knives of flint or bamboo, and extract the babies for eating [7].

## MEDICAL TREATMENT

The first thing to remember when considering the treatment of disease is that it had a magical basis and that in the mind of primitive man drugs acted not by their intrinsic merits but because they were the vehicles of a benign spirit.

The remedies employed can be divided into animal, vegetable and mineral. Of the minerals gold, in the form of an infusion, was used to treat epilepsy; silver, applied to contusions, prevented ecchymosis; magnetic oxide of iron in the form of powder dissolved in water, was used to treat nervous and cardiac affections; *ccolpa* or *millu*, a flux, was used as a purgative, as a liniment, as a caustic for ulcers, and in the procedure known as *millipña* or *ccolpasca;* sulphur to combat "air in the head"; lead sulphate, or *hancu-ccollque*, dissolved in water, for shock; orpiment or realgar for poisoning; *greda*, or emetic clay, to arrest

# Section of Pædiatrics

President—A. DOYNE BELL, M.A., D.M., F.R.C.P.

[*January* 24, 1958]

## DISCUSSION ON THE PREVENTION OF ACCIDENTS IN CHILDHOOD

**Dr. C. A. Boucher** (London) read a paper dealing with the incidence of accidents, present trends in their frequency, and measures of prevention. With his permission the following tables are reproduced from his paper.

TABLE I.—FATAL ACCIDENTS IN CHILDREN—HOME AND ROAD

| | 1951 | 1952 | 1953 | 1954 | 1955 | 1956 |
|---|---|---|---|---|---|---|
| Home .. .. | 1,069 | 956 | 838 | 793 | 809 | 796 |
| Road .. .. | 914 | 786 | 797 | 662 | 764 | 717 |

TABLE II.—DEATH-RATE PER MILLION FROM ACCIDENTS AMONG CHILDREN UNDER 5 IN ENGLAND AND WALES 1950–54 (APPROXIMATE)

| | Age (years) | | | | |
|---|---|---|---|---|---|
| Cause | 0– | 1– | 2– | 3– | 4–5 |
| Scalds and burns .. | 28 | 49 | 42 | 37 | 28 |
| Drowning .. .. | 7 | 33 | 51 | 43 | 33 |
| Falling, crushing .. | 18 | 21 | 20 | 16 | 9 |
| Motor vehicles .. | 6 | 50 | 95 | 100 | 98 |
| Suffocation .. .. | 749 | 42 | 9 | 4 | 2 |
| Poisoning .. .. | 7 | 35 | 12 | 8 | 5 |

TABLE III.—FATAL HOME ACCIDENTS (1955)

| | |
|---|---|
| 0–1 year .. | 480 |
| 1–4 years .. | 212 |
| 5–14 years .. | 117 |
| Total | 809 |

TABLE IV.—FATAL HOME ACCIDENTS (1955)

| | 0–4 years | 5–14 years |
|---|---|---|
| Poisoning .. .. .. | 22 | 2 |
| " (gas) .. .. .. | 18 | 5 |
| Falls .. .. .. .. | 38 | 13 |
| Burns .. .. .. .. | 67 | 64 |
| Scalds .. .. .. .. | 35 | 1 |
| Electricity .. .. .. .. | 4 | 3 |
| Drowning .. .. .. .. | 13 | 3 |
| Suffocation .. .. .. | 415 | 8 |
| Others .. .. .. .. | 80 | 18 |
| Totals | 692 | 117 |

TABLE V.—COMMONER POISONS CAUSING DEATH IN CHILDREN UNDER 10 YEARS IN ENGLAND AND WALES

| 1931–5 | | 1950–2 | |
|---|---|---|---|
| Poison | No. of deaths | Poison | No. of deaths |
| Belladonna (vegetable and medicinal) | 8 | Ferrous sulphate | 24 |
| Caustic soda (?+"corrosive" 2) | 7 | Antihistamines | 19 |
| Strychnine | 6 | Aspirin | 15 |
| Disinfectants | 5 | Strychnine | 12 |
| Camphor | 5 | Lead | 7 |
| Ammonia | 4 | Oil of wintergreen (liniment of methyl salicylate, BPC) | 6 |
| Oil of wintergreen (liniment of methyl salicylate, BPC) | 3 | Digitalis | 5 |
| Digitalis | 3 | Barbiturates | 5 |
| Morphine | 3 | Caustic soda | 3 |
| Aspirin | 3 | Morphine | 3 |
| | | Kerosene | 3 |
| | | Methadone | 2 |
| | | Phosphorus | 2 |

Dr. Boucher continued by saying that a great deal of publicity had been given to this subject through films, the radio, television, leaflets, women's magazines and, last but by no means least, The Royal Society for the Prevention of Accidents. This publicity was bringing results, but more needed to be done through general and personal education, particularly of parents of young children, and of older children themselves. It was the personal influence of the general practitioner, the medical officer of health, the hospital doctor, and their agents, the home nurse, home help, and health visitor which must ultimately prove effective.

**Mr. D. MacG. Jackson** (Birmingham): Basic fact-finding work, which is the foundation of accident prevention, is being carried out in this country largely by the Royal Society for the Prevention of Accidents, by the Ministry of Health, different Government Departments, the British Standards Institution, the Fire Research Board, the Fire Protection Society, the police, and by interested individuals, several of whom have been doctors. In 1956, the World Health Organization formed an Advisory Group on the Prevention of Accidents in Childhood to study methods of fact-finding, and to evaluate and co-ordinate related data. Their first report makes most interesting reading and should certainly be read by doctors working with children (Accidents in Childhood, 1957).

The general principles of accident prevention are conveniently classified in this publication under the three internationally accepted E's—Education, Engineering and Enforcement by regulation and law. "Education" includes the training of children and the teaching of parents. It also includes making drivers of motor vehicles aware of special risks and keen to drive with a high standard of care. "Engineering" includes not only improving the design of houses and roads to prevent accidents, but is a convenient heading under which to include all changes in design and manufacture of cars, furniture, clothes and toys, to make them safer. Only when propaganda, the provision of facilities and public opinion fail to get safety measures accepted is "Enforcement" by legal measures necessary. But where continued inertia and economic considerations encourage a laissez-faire attitude, legislation may be the only effective measure.

The three chief causes of fatal accidents in childhood in England and Wales are, first, motor vehicle accidents, followed in frequency by burns in girls and drowning in boys. Other accidents in the home are less lethal to children but much commoner, and include scalds, falls out of bed, off furniture and on stairs, and injuries by domestic machinery and from doors. The following is a brief survey of adopted and suggested preventive measures for two of these types of accidents, namely motor vehicle accidents and burns, mentioning only those features which are related to child accidents.

## MOTOR VEHICLE ACCIDENTS

In 1956 there were more road vehicles licensed in Great Britain and more people hurt on the roads than ever before, but there were fewer child fatalities than in any year except 1954. The main contributors to this decrease were child pedestrians (Road Accident Statistics, 1956). However, there are still nearly 50,000 children becoming road casualties each year.

*Education.*—Fig. 1, shows the period in life during which a child is at great risk as a pedestrian (3–12 years), and as a pedal cyclist (12–21 years). This emphasizes forcibly the importance of training children from a very early age in how to behave as pedestrians in modern road traffic, and this should later be extended to how to cycle on the road. The responsibility for training falls primarily upon the parents and upon schools, but many organizations are playing a part. A game called "last across the road" used to be played in this country by school children and consisted in dashing across the road in front of oncoming traffic, the smaller ones sometimes falling and becoming casualties. This dangerous game has been practically eliminated by preventive instruction in schools (Accidents in Childhood, 1957). The "Mind that Child" Campaign, September–November 1956, is claimed to have played a part in making 1956 the second lowest annual total of child road deaths on record; and last year the "Road Safety Matters" Campaign was conducted throughout the country. There have been many local campaigns of which the Slough Two Year Road-Safety Experiment has probably been the biggest.

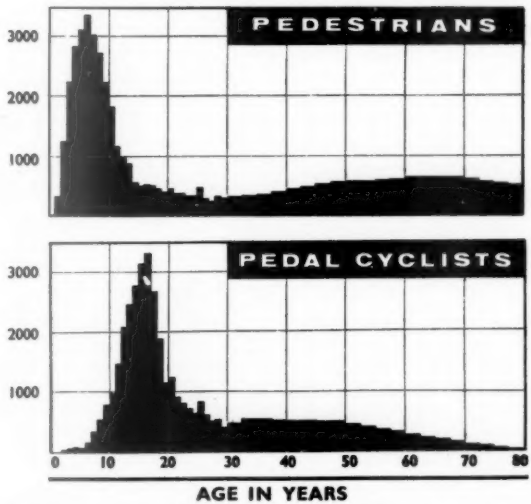



FIG. 1.—Pedestrian and pedal cyclist casualties according to age in 1956. (From Road Accident Statistics, 1956 (1957). Royal Society for the Prevention of Accidents. By courtesy of the Editor.)

If parents are to train their children, they too must be made aware of the risks their children run on the road. The Press plays a big part in this education programme whenever a news item presents the opportunity, and much useful propaganda is also absorbed from radio and television programmes. B.B.C. Television, which at peak times reaches 1 in 3 adults in Great Britain, is very alive to the problem. Recently in 77 days there were 61 items of road safety interest. Again, short film flashes between main features at the cinemas can be a most impressive reminder in graphic form.

The education of drivers is a much more subtle business, for every man will claim to be an expert driver if he is more than ten miles from home. There are at least two ways in which a driver may have impaired judgment and ability, *without knowing it*. The first is the ill-understood phenomenon of skill-fatigue. The following description of it appeared in a recent *Lancet* editorial (*Lancet*, 1957*a*). "In the driver its earliest symptom is a slight change in the timing of his reactions. . . . Classically the night driver halts at an intersection where there is no traffic light and waits patiently for the green; then, 'pulling himself together', he flashes on, intent on the clear roadway ahead, and deriving no meaning from the headlights he sees approaching from the side." Skill-fatigue is not necessarily accompanied by physical tiredness, and in fact most road-transport accidents occur in the first three hours of the journey. Awareness of the entity of skill-fatigue should make those who know about it more careful and more safe.

Alcohol is the other serious cause of impaired driving standards, and again I quote from the same editorial (*Lancet*, 1957*a*). "Controlled studies in Sweden have shown that very small quantities significantly increase driving errors committed even by first-class motorists. Indeed much driving experience and a little alcohol may be one of the deadliest combinations. It is also worth bearing in mind that, though rapidly absorbed, alcohol is eliminated from the body very slowly, and that it may linger in relatively high concentrations in the cerebro-spinal fluid and in brain-tissue many hours after the blood-alcohol level has returned to normal. (Most airlines require that pilots shall abstain from alcohol for at least eighteen hours before flying.) None of the popular remedies—exercise, a cold bath, strong black coffee—has the slightest effect on the slowed reactions, impaired judgment, and lack of insight of the alcoholic driver." I do not know the incidence figures in this country, but in the U.S.A. in 1956, 40,000 people died in road accidents and "a drinking driver" was involved in 30% of these fatal accidents. 20% of all pedestrians killed were reported as "had been drinking". (Road Accident Statistical Review, 1957.) The meaning of these terms is uncertain, but even if a causal relationship is established, can people be persuaded to accept the general rule "I don't drink before driving"? Public opinion varies in different countries, depending in part on the value put on personal liberty and the safety of others.

*Engineering, design and manufacture.*—Most changes contemplated in this field at present are of general preventive value and include children only incidentally. Much work is now going ahead on the improvement of roads and the provision of bridges, islands and crossings. Separate cycle tracks—such a good feature on many continental roads—should surely be provided more often in this country, and their use by cyclists made compulsory. One hopes that improvements in car design will really materialize from the findings of the Cornell University team. Features of car design at present responsible for fatal accidents to passengers, including children, are lack of safety belts, accepted long ago in air travel, and inadequate safety-locks on doors to prevent ejection from the car in roll-over and other accidents: severe-to-fatal injuries were four times less common in road accidents in a group of cars provided with safety belts than in a comparable group without (*Lancet*, 1957*b*). Other changes in car design to improve vision, especially where the windscreen and driver's side-window join, and better seat adjustment to include elevation as well as forward and backward movement are called for. Safe dipping and antidazzle arrangements are a common topic for criticism and suggestion in the daily papers at present, and dashboard layout seems often designed more for symmetry than for safety. To switch off the headlamps at night by mistake for 1 second, while intending to light a cigarette, means driving blind for 60 feet if the speed of the car is 40 miles per hour.

*Enforcement.*—In this democratic country in peacetime controls are only initiated and accepted when public opinion is ready to accept them. This has advantages in reducing the number of regulations but it makes for slow progress in reducing accidents. Limitation of parking for a safe distance before pedestrian crossings has been accepted without difficulty. So has the closure of some unessential streets to traffic in thickly populated areas, so that they may become the safe and only playground of the many children whose houses open on to them. Is it time yet to legislate to prevent all traffic parking on a country road? In the United States all traffic parking in the country must get off the road. Again, should parking be prohibited within 30 yards of a road intersection *everywhere* (Gissane, 1954)? Would compulsory use of pedestrian crossings with red and green lights in all built-up areas be regarded as impossibly harsh? At present, almost certainly it would. Should child cyclists have regular cycle inspections at school or by the police? Sometimes one sees children riding pillion on motor cycles without crash helmets. Crash helmets reduce the chance of head injury in an accident by 30–40%, and the wearer has a 50% better chance of survival in non-built-up areas, and a 25% better chance in built-up areas (Road Accident Statistical Review, 1957). With this evidence should crash helmets not be compulsory? Fact-finding studies are called for first to confirm the size of these risks, and enlightened legislation may then be required to secure adequate protection from them.

## Burns

It should be remembered that children are the group most seriously affected by burns. At the Burns Unit in the Birmingham Accident Hospital, over half the domestic burns and scalds serious enough to be admitted are children under 15 years, and one-third are under 5 (Colebrook *et al.*, 1956). Again, a study of burns in which clothes were set alight provides the following comparison, after correction of age groups for population. If the incidence

of clothes-alight burns in adults from 15–64 years is taken as a standard, then children from birth to 4 years have ten times as many burns, and schoolchildren from 5–14 years six times as many (Bull, 1958).

The Registrar-General's figures of deaths from burns and scalds for 1956 show 741 deaths—a drop of 8 below the average figure for the period 1952–56. There were 11 fewer deaths from burns in childhood in 1956 (134) than in the previous year (145), but although this is in the right direction it is of doubtful significance. There has been little change in this picture in recent years. It is still true, as the *Lancet* wrote in 1946, that "in the homes of the people we neglect the most elementary precautions against accident, and wantonly permit hazards that would cause a public scandal in the most primitive factory or workshop".

The preventive measures that should be taken can again be considered under the three E's.

*Education.*—Tempest has demonstrated recently the appalling ignorance of parents, medical students, doctors and nurses about the risks of inflammable clothing and their responsibility to guard fires (Tempest, 1956).

Unguarded fires are the commonest cause of domestic burns and together with inflammable clothing are responsible for the great majority of fatal burns in childhood. The facts to be driven home in the minds of parents are:

(1) Adequate fireguards are the first step towards making the home safe from burning accidents. The guards should pass the British Standard Specification and should be capable of being securely attached to the fire-surround. Parents should be told where these can be purchased and how much they cost. Exhortations without this information carry little weight.

(2) Parents should know that if their child under 12 years suffers serious injury or death through burning or scalding due to an open unguarded fire, they can be prosecuted and fined up to £10. This adds a further incentive to do something without delay.

(3) They should know that by law all new gas, electric and oil heaters sold after October 1, 1954, must be fitted with a guard which complies with special safety specifications, and, probably more important, that safe guards can be bought for the old fires which they had before 1954. Again they need to be told where these can be obtained and the cost of them.

(4) Some Local Authorities hire safe guards to parents of young children. Where this applies it needs, of course, to be made widely known.

Tempest's study showed that sound radio and television programmes were by far the commonest sources of information in the case of parents who knew these facts. Other means of education used in Birmingham are regular reporting of burning accidents by the Press, film flashes in cinemas between features, warning posters in buses, exhibitions by the Royal Society for the Prevention of Accidents, lectures to Women's Institutes by doctors, nurses and others, the distribution of warning and information leaflets by health visitors, and the display of photographs of burned patients, with captions, in street windows by the Fire Service. Many people have fireguards, of a kind, which are rarely used, so that constant reminding *to use them* is valuable.

The second educational measure is to spread knowledge about the safety and dangers of certain fabrics. Clothing alight is a feature of half the burns admitted to the Birmingham Burns Unit, and it is a feature of four-fifths of the deaths. Nightdresses and dresses were about equally responsible in Tempest's study, loose-fitting clothing which stands away from the body being much more dangerous than pyjamas.

With regard to clothing materials, the information that parents should be given is that:

(1) Flannelette and winceyette, like other forms of cotton and rayon, are very inflammable. These materials, being cheap and attractive, account for four-fifths of the clothes-alight injuries and nine-tenths of the clothes-alight fatalities. Wool and silk do not burst into flame in the same way, but smoulder. Man-made yarns like nylon and terylene are inherently safe, and are marketed in many attractive forms and designs.

(2) Some materials which burn easily, such as cotton and rayon, can now be rendered relatively flame-resistant by chemical processes which withstand repeated washings and are not toxic if sucked by children. The efficiency of the process is established, but until recently there has still been some impairment in the texture of lighter weights of material.

(3) Some less-used materials are particularly inflammable. In New Zealand recently public opinion was shocked by the death of a well-known physician's wife whose ball dress of highly inflammable lacquered net touched an unguarded electric fire. Another new and particularly dangerous material is composed of waste fibres bonded together with latex; this is claimed to be suitable for stand-out petticoats under full skirts and is highly inflammable. The flammability of any material can be tested using a small piece from the seam of the garment.

Propaganda pressing home these points must be continued and pointed. Leaflets and posters can be displayed in Infant Welfare and School Clinics. Sixth form girls at school should themselves be taught the preventive measures for home accidents, and they should see displays of safe fireguards and safe fabrics with the names of shops where they may be bought.

*Engineering, design and manufacture.*—There is immense scope in this country for improved house design, especially in relation to heating; but while open fires continue to be used there will be no safety without the regular use of efficient fireguards, and these are available. But efficient fireguards need firm attachment to the fire surround, and in spite of recommendations for this by the Minister of Housing in 1949 few local authorities have so far provided such fitments in their new council houses.

Overcrowding is a fundamental contributory cause of home accidents, including burns, which can only be reduced by increasing the number of good council houses; and linked with this should be improved kitchen design, particularly in the arrangement of the cooker and sink, so that boiling water does not have to be carried across the crowded living room several times a day.

On the textile front, firms should be encouraged continually to produce an increasing range of safe fabrics, using inherently safe materials at present, and, when perfected and available, flame-proofed cotton and rayon also.

A large degree of safety can be obtained simply by dressing girls in pyjamas rather than nightdresses, and at least one large national store has stopped selling nightdresses for this reason. Others should be encouraged to follow suit.

*Enforcement.*—The prosecution of parents and guardians whose children under 12 are seriously injured or die due to unguarded fires is not often carried through. After a warning it is usually felt that they have suffered enough and have learned their lesson—although too late.

Apparently no legislation exists to prevent the import or manufacture of extremely dangerous materials, such as lacquered net, or to ensure that buyers are warned of their danger. As soon as a workable standard is accepted by the British Standards Institution it should be possible to mark material with its flammability rating, and this warning should be made compulsory.

It is to be hoped that the all-Party Parliamentary Home Safety Group which has been formed will attend to necessary legislation as new evidence of preventable risks calls for it.

If the fitting of efficient guards to old electric, gas and oil fires could be made compulsory, there is good reason to believe that many deaths and much suffering would be avoided.

The statistical and scientific approach is well suited to *investigation* of the accident problem, but it is useless to touch the hearts of many people and to goad them to action. On the other hand, the tragic, individual case, with its peculiar hardships faced with quiet courage, is equally useless as a basis for planning wholesale preventive measures. But if the individual case is representative of common risks, and is well presented, it may kindle such deep concern in the hearts of hearers that parents will go out and buy a fireguard, and doctors will notice and speak out when they see children surrounded by needless domestic risks. Many decry the value of emotion to strike through indifference and inertia, but for many people emotion is a much more effective spur to action than intellectual knowledge and should be used as a good servant. It is a peculiar idea of intellectual integrity to believe one must use the same language and approach to the harassed mother and to the research statistician.

How can we "get through" to knowledgeable, influential, and good-hearted people who meet statistical data with the attitude "Accidents will happen!"—"You can't wrap children in cotton-wool!"—"We all have to learn the dangers of our environment the hard way." We need to enlist the help of the leaders of the textile industry, the retail trade, the electricity and gas boards, and local authorities. I believe we must show them injured children, in hospital or pictured, to clothe the statistics with personality and make them live.

Here are statistics—"Ten thousand children are severely injured on the road each year, and 700 more are killed". Now I want you to meet Janice (Fig. 2). She was 5 years old. She was knocked down by a car and her leg run over. She had to lose her leg. Did she have to learn her road-sense this way? If she had been your girl, would you have felt that a little teaching about road safety would have been "wrapping her in cotton-wool?"



FIG. 2.—Janice, aged 5. She lost her leg after being knocked down by a car. (By courtesy of Mr. William Gissane, 1954, and the Editor of the *Practitioner*.)



FIG. 3.—Dorothy, aged 5. Her clothes caught alight from an unguarded coal fire.

Or again, here is Dorothy, aged 5 (Fig. 3). Her cotton dress caught alight from an unguarded coal fire. She tried to get it off over her head but did not manage it. It burnt out. Her face is terribly scarred for life. Of course it could happen to any girl with a dress of inflammable material who was put to live in a room with an unguarded fire. But one cannot help wondering—Did she have to learn the dangers of her home environment in a way so costly, and so final?

Even disability and disfigurement do not always measure the full tragedy of a child's accident. Recent work in the Birmingham Burns Unit by Woodward (1958) has shown that out of 200 children admitted between 1952 and 1955 with burns of more than 10% of the body surface, 85% still show signs to-day of emotional and mental disturbance in the form of fears and anxieties, depression and lethargy, aggression or unsociability—sometimes with added psychomatic disorders such as enuresis and stammering. Some people are more touched by this aspect, as well they might be.

To most people children matter. For many accidents in childhood methods of prevention are to hand. What is the necessary ingredient which will change the still prevailing attitude "Accidents will happen" to the determination "Accidents won't happen"?

## REFERENCES


Accidents in Childhood: Facts as a Basis for Prevention (1957) *Tech. Rep. Wld Hlth Org.*, No. 118.
BULL, J. P. (1958) *Med. Pr.*, **239**, 205.
COLEBROOK, L., COLEBROOK, V., BULL, J. P., and JACKSON, D. M. (1956) *Brit. med. J.*, i, 1379.
GISSANE, W. (1954) *Practitioner*, **172**, 620.
*Lancet* (1946) ii, 833.
*Lancet* (1957*a*) ii, 627.
*Lancet* (1957*b*) ii, 990.
Road Accident Statistical Review (1957) **2**, No. 18. Royal Society for the Prevention of Accidents, London.
Road Accident Statistics, 1956 (1957) Royal Society for the Prevention of Accidents. London.
TEMPEST, M. N. (1956) *Brit. med. J.*, i, 1387.
WOODWARD, J. (1958) Personal communication.

**Professor S. D. M. Court** raised the question of what was a "significant" accident. Referring to the Thousand Families Study in Newcastle he said they had come very near to Clements' definition of a significant accident as one that was serious or could have been serious in slightly different circumstances. In the first five years of life the 847 children in the families had had 732 accidents accounting for 9% of their total illness; but only eleven were admitted to hospital. About half the accidents were falls, one-sixth burns and scalds and the remainder divided equally between "crushing", "traffic" and miscellaneous injuries. They had been unable to demonstrate any special risks or personal proneness to accidents which were not explained by differences in sex, living conditions and maternal care. Propaganda addressed to parents and children, though necessary, he thought more limited in its effects than generally realized. If child protection was to become part of the structure as well as the attitude of society, it should be addressed primarily to the designers and manufacturers of houses, fittings, clothing and all potential dangers in the environment of children.

REFERENCE

CLEMENTS, F. W. (1953) *Med. J. Aust.*, i, 348, 388, 421.

**Dr. L. Colebrook** agreed with a previous speaker that the public was often misled by the labelling of a material, or a garment, as nylon (a relatively safe fibre) when in fact it was a mixture of nylon with cotton or another more flammable fibre. It would be an important step towards safety if all clothing materials and garments were required by law to carry labels stating correctly their composition. The public was becoming more safety-minded. It would soon learn which materials were relatively safe, and which dangerous.

**Dr. D. MacCarthy** said that when a serious accident happened to a child there was at the same time an accident or at least a danger to his developing personality. Here was a field of prevention if treatment could be begun straight away. But the difficulties of going about it, say in a 2-year-old severely burnt child, were admittedly great. Did anyone know how to go about it? Was anyone doing it?

# Section of Obstetrics and Gynæcology

President—Sir ARTHUR GEMMELL, M.C., T.D., M.A., M.D., Hon. M.M.S.A., F.R.C.S.Ed., F.R.C.O.G.

[*February* 28, 1958]

## DISCUSSION: EARLY DIAGNOSIS AND CANCER EDUCATION OF THE PUBLIC

**Mr. Malcolm Donaldson** [*Abstract*]:

To obtain early diagnosis in malignant disease is largely a psychological problem. True cancerphobia is rare but nearly 100% of the population suffer to a greater or less extent from cancer apprehension, which may take one of two forms: (A) Personal apprehension in which case the patient thinks "can this be cancer?" when a symptom is experienced which is not easily explained, e.g. a slight pain in a woman's breast. (B) Impersonal apprehension where a person fears that by speaking of the disease or even mentioning the word, fear will be caused in the person addressed. There is now overwhelming evidence in every country where cancer education is carried out, that this latter is NOT true. In spite of this many doctors in this country suffer from "impersonal cancer apprehension" and this does untold harm by keeping up "hush-hush and a conspiracy of silence" which is largely responsible for the delay in seeking advice in the accessible cancers and these as a rule do show symptoms whilst the disease is still in an early stage. For example, the average delay after noticing symptoms in carcinoma of the rectum is thirteen months, uterus six months, and breast seven months. Figures published recently by the Registrar-General show that six months' delay reduces the number of early-stage cases from 71·6% to 46·7% which means the loss of thousands of lives.

*Statistics.*—Positive statistical evidence of the value of cancer education is very difficult to obtain for many reasons, e.g. the fact that such education is discouraged by doctors in this country, and that the clinical records are inefficient in most hospitals. There are other difficulties; for example, the unknown factor of the rate of growth and malignancy in any individual tumour. This shows itself if the five-year survival rate is used as a criterion as is seen in the following figures from Manchester:

| *Delay in months* .. | 0–3 | 4–6 | 7–12 | 13–24 | 24+ |
|---|---|---|---|---|---|
| *Five-year survival*.. | 44% | 39% | 41% | 39% | 44% |

This, of course, is a comparison of entirely different types of growths. In the early months the majority of tumours are rapidly growing and highly malignant, whereas after two years the growths are entirely slow-growing almost benign tumours, a selection by death. This difficulty of the "unknown factor" can be largely avoided by comparing the records obtained over many years, of the delay in reporting certain symptoms, e.g. lump in the breast, uterine bleeding, rectal bleeding, &c., *whatever the cause of the symptom*, and the percentage of "early stage cases of cancer" treated during the same years of cancer education. If the delay diminishes and the percentage of "early stage" cases treated increases, then there can be no doubt of its value. Figures obtained from Canada and elsewhere are very suggestive of the value of cancer education.

*Attitude of public to cancer education.*—The public are interested in the subject of cancer and lectures are popular. 74 were given in the Oxford area with an average attendance of 3[illegible]·2 per lecture during 1947 and 56 are booked for 1958. In Yorkshire of 5,740 ballot papers filled in at the end of lectures 99·1% voted in favour of more lectures, 0·2% against and 0·7% put a ?.

*Reaction of medical profession.*—Result of British Empire Cancer Campaign questions to all general practitioners 1953: Only 24%–25% replied and of these 2,683 voted against, 2,370 voted for Cancer Education. Few have had any experience, and many are very prejudiced.

*Method of carrying out cancer education.*—Word of mouth is the best; lectures by doctors, but these can only be few. Information passed on by nurses is the only practical method; they are the first line troops of any campaign. Other aids are pamphlets, page-turning machines, films, &c.

## Conclusions

From the psychological point of view cancer-education is of very great value to the nation and will save a number of lives. It has well been said "It is better to die of cancer than to live in fear of it", but it is better still to do neither.

"Knowledge is the antidote to Fear."
*Emerson.*

**Dr. John Burton:**

In the last ten years since I have been engaged in Health Education, cancer control has been an ever-present problem. Clinical statistical evidence and the behaviour of surgeons has caused me to assume that cancer control can be based on prevention and early treatment.

In the gynæcological field there are very few clues to prevention. As one whose job it is to help people to help themselves, my interests have been centred on early treatment.

It is generally the patient who makes the first diagnosis; the patient and friends who decide what to do about it, whether to visit a doctor or a quack or neither. It is the patient and friends and even employers who decide whether she will accept treatment and carry it out. The medical profession is remote from these decisions. The events I am most interested in are those which take place within the bosom of the family in casual conversation, concealments, and reticent understatements and in rationalizations of committees responsible for treatment or disseminating information.

Apart from any measure of environmental control which may be profitable, most promising lines of cancer control involve some major change in human behaviour, which, of course, means education. For the public health world the problem of cancer control is one of environmental control and education. It is education of the medical profession, of Members of Parliament, of public men such as councillors and also of the general public. The attitudes of optimism or despair, and the feelings of confidence or fear in such people may be an important determining factor in whether anything is achieved.

The outstanding problem to be faced is the emotional climate in which this disease exists: the fear of fear: it constitutes a major resistance to doing anything in committees and we have seen it obstructing in all sorts of organizations which should know better. For many years the official view of the Ministry of Health was that cancer education should not be carried out, for fear of creating cancerphobia in the public.

What we have done is to shift our own fears on to the shoulders of the long-suffering public and say that it is they who are frightened when really it is ourselves. We have met the same problem in the medical profession, and a recent vote of general practitioners on the subject of cancer education registered a 50–50 for and against. We have come across the same problem in research organizations which will not touch the subject of cancer education. Every argument has been used to avoid public discussion on this fearful thing.

We have not, curiously enough, met this fear of fear among the populace. I have addressed many ordinary meetings and given information about cancer and the reaction has been "What is all the fuss about?" "Why are people going around with long faces and behaving as if this were something special?" The general public, on the whole, are much more prepared to accept Clough's paradox "If hopes were dupes, fears may be liars" than we are.

The individual reasons encountered for doing nothing are to regard the whole matter as something distasteful or which "couldn't possibly happen to me". The childish hope that symptoms, if ignored, will pass away, is also encountered. There are also those whose self-respect is bound up with not having a day's illness, and some even seek relief in regarding cancer as a punishment for bad living and an expiation of guilt.

The suggestion has been put forward that special clinics should be set up like the tuberculosis clinics, where people could drop in almost secretly and have an examination. This is something that the Health Service may have to bear in mind in any planning—that it is no use having cancer education if people do not feel happy about the place where they have to go to declare their symptoms.

*What positive steps can health workers take in education?*—First we must be sure that the story we tell is true and, in accordance with the Hippocratic oath, does no harm to our patients. We must be satisfied that cancer education does not cause cancerphobia and that the information we put forward is well backed up by evidence.

In the case of prevention there are already sufficiently well established facts on which to base action. There is strong evidence that the personal hygiene of the husband plays an important part in the risk of cancer of the cervix in the wife. The connexion between smoking and lung cancer is well established. The case against atmospheric pollution is a strong one, as is also the case for breast feeding in the prevention of cancer of the breast. X-raying pregnant women appears to increase the risk of their children developing leukæmia.

In relation to early treatment, we are not yet in a position to be dogmatic, because there are still two main points of view between which we have to choose. The first proposition contends that there is, as yet, no satisfactory evidence that cancer treated early does better than cancer treated with delay, and that therefore however effective cancer education may be in cutting down delay, the end-results are the same. If this argument is carried to its logical conclusion it must mean that treatment at present given is worthless. The only sensible thing to do would be to pack up, save the money and spend it on research. In practice, however, I have yet to meet the surgeon who does not try to get his patients as early as possible.

The other more hopeful proposition is that cancer in certain sites definitely does better when treated in the early stages. The sooner patients see their doctors after noticing something wrong the more likely are they to be cured.

That two such diametrically opposed hypotheses can exist raises the question: Why has the Medical Research Council, or some similar research body, not yet been asked to test these opposite assumptions on which the lives of upwards of 80,000 people depend each year? We appreciate that it is not easy, but the problem is of such magnitude as to warrant the utmost effort. Research work will have to be done which they should commission. Ideally it should seek to establish, firstly, the degree to which early treatment affects the chances of cure; and secondly, the effectiveness of education in causing people to take certain symptoms to the doctor early.

The first aim can only be achieved if experiments are designed specifically to reveal the relationship between early stages of the disease and early recognition by the patient. The second can only be demonstrated if general practitioners are prepared to make a special enquiry and record of anyone complaining of certain designated symptoms whether they turn out to be cancer or not. Any one, or any group of symptoms, can be chosen for education and recording, and a before-and-after study carried out. Some well-placed authorities consider that such experiments would be too difficult to interpret and that finally the only useful experiment would be an educational programme followed by an assessment of any changes in cancer mortality.

**Mr. C. J. Thurgar:**

In the past the advocates of education of the public regarding cancer have, in my opinion, tended to make rather optimistic claims for improvement in the survival rate if the disease is recognized and treated within a short time of the appearance of the first symptoms. It is equally true that opponents of cancer education appear to have exaggerated the danger of increasing the incidence of cancerphobia. I include myself in those who have set their hopes too high and have claimed too much. I first became interested in cancer education in 1936 and started with some of my colleagues in Newcastle upon Tyne a programme of lectures to lay audiences, large and small. It was soon found that large meetings were not a success and our efforts were concentrated on Women's Institutes, Rotary Clubs and the like. Several hundred such talks were given in the ensuing two or three years before the outbreak of war and in 1939 a booklet was published on the early diagnosis of cancer by the North of England Council of the British Empire Cancer Campaign. At the beginning a large number were sold but the sales rapidly tapered off and apart from distribution at meetings and talks, it was withdrawn in 1940. Two mistakes were made in the conception of this booklet. It included an appeal for donations to cancer research and it claimed too great a success in the sense of cure from early diagnosis and treatment, both in the number of sites of malignant disease listed and in the survival rates expected. The talks to small gatherings have been continued on a much reduced scale over the intervening years and have been well received as is shown by requests for repetition to the same groups after the lapse of an interval.

It is difficult to gauge whether these efforts have had any effect in North Eastern England of either a beneficial or a harmful nature. My impression—and it is only an impression—is that patients have occasionally consulted their doctors at an earlier date than otherwise would have been the case, but such information is very rarely volunteered either to the general practitioner or to the consultant. No instances of the production of cancerphobia have come to light and my experience is thus in line with that of other workers in the field of cancer education. In retrospect it appears to me that our programme was too widespread and lost some of its impact because we did not invite the co-operation of the general practitioners of the area.

Increasing familiarity with the natural history of the cancerous group of diseases and study of the mortality figures for our own population of 3 millions lead me to conclude that only a very limited field is available for honest and optimistic education. Healthy people do not want to talk or think about illness, which they may view with interest but not normally with personal concern. The fear of cancer, although emotional rather than rational, is

based on reality. The death-rate as a whole is rising, though there are wide variations in the mortality with the site of the primary tumour. How then, should an educational programme be planned to take account of these factors? It can be directed to three aims; the prevention of the development of cancer, the early diagnosis of those who have symptoms and the detection of cancer and precancerous conditions in the population as a whole before symptoms have appeared.

The prevention of cancer, apart from its industrial applications, is not fraught with great hope. We are not rational beings and I myself continue to smoke large numbers of cigarettes despite my full recognition of the possible hazard. A surgical colleague said to me "I should hate to give up smoking and then die of carcinoma of the rectum!" Far more people give up smoking for economic reasons than because they are concerned with the possibility of developing lung cancer in twenty or thirty years' time. To exhort women to feed their children on the breast rather than the bottle is similarly liable to consideration in terms of expense or expediency rather than of long-term prudence.

Early diagnosis of those with symptoms is in practice limited to sufferers from the accessible cancers—the skin, tongue, mouth and throat, breast, uterus and to some degree bladder and rectum. The bladder and the rectum are sites where education could perhaps best be directed as much or more to the medical profession than to the public. Skin cancer is not nowadays a real problem nor a contributor to mortality figures and squamous carcinoma of the head and neck and particularly of the tongue and mouth, has declined in incidence to nearly half of what it was twenty-five years ago. There is room for education here, but its effect will not be great in numerical terms.

Diametrically opposed views have been expressed very vocally in recent years regarding the effectiveness of treatment in breast cancer, ranging from the statement that it has *no* effect to claims that 75% of women could be cured if they presented for treatment while their growths were small and limited to the breast. The prospects of increased survival from early treatment can be gauged from the figures just published from Birmingham, where 49% of patients who were treated within one to two months of their first symptom, irrespective of stage or grade, were alive and well at five years, whereas only 39% survived five years if they delayed for six to eleven months. After one year, there was little variation in the survival rate. It may be that in cancer of the cervix uteri, an improvement of more than 10% would be found, but I have no reliable figures and the incidence of cancer of the cervix is only half that of breast cancer.

In my own regional figures, cancer of breast and cervix accounts for about one-sixth of the total incidence of malignant disease. There are 90,000 deaths annually in England and Wales from cancer and if one-third is added to cover successful treatment, probably an optimistic figure, an incidence of 120,000 per annum results. One-sixth of this is 20,000 and ten per cent of that is a gain of 2,000 women alive and well at five years. A considerable proportion of these would die from recurrence of growth after five years but the gain would still be very substantial. An additional 1,000 men and women could probably be salvaged from the many other forms of cancer by effective education on a national scale. I regard this hypothetical figure of 2,000 to 3,000 as a maximum and I doubt whether it could really be achieved. If it can, it is still no matter for great congratulation when set against 90,000 deaths a year.

There remains the possible trial of cancer detection clinics and mass screening techniques. Simple clinical examination of the mouth, breast, &c., either by the doctor or the patient presents few difficulties other than psychological ones, but most normal people would not want to be cystoscoped or be examined rectally once a year. The most hopeful method in sight at present lies in exfoliative cytology and this form of examination is most easily and reliably applied in the field of gynæcology.

In conclusion, it is my view that nation-wide and intensive cancer education, primarily to small audiences and supported by judicious press publicity, would have an appreciable effect in time upon the number of lives saved or prolonged, but the effort needed would have to be far greater and longer continued than is generally realized. In terms of its impact upon the total cancer death-rate, the effect would be comparatively slight. That is not to say that the effort should not be made, but too optimistic forecasts of its result must not be advanced until much better methods of early diagnosis and treatment are evolved than those at present available.

**Mr. John Wakefield:**

Much opposition to the idea of cancer education has sprung from the well-meaning, but vague, proposals put forward by enthusiasts. Doctors are not so much concerned to decide if cancer education is a good idea in principle; they want to know what its effects will be on them and on their patients. When asked to approve any proposed scheme of lay educatio

they must be told what information is to be given, how it is to be put over, and what safeguards are proposed against undesirable results. Only then can they assess the likely advantages and disadvantages of cancer education.

In the project conducted by the Manchester Committee on Cancer in Lancashire and Cheshire, every extension of the original pilot experiment has had ready support from all branches of the medical profession, once our proposed activities were explained and discussed in advance. A recent survey in the area where intensive education has been going on for six years (Wakefield and Davison, 1958) showed that the project had earned the almost unanimous approval of general practitioners.

The hub of the Manchester scheme is the panel of speakers—mostly specialists in the treatment of cancer—whose members give regular, short, informal talks to all lay groups in the area. There are no large public meetings, which tend to attract hypochondriacs and the unduly health-conscious, and stifle the easy flow of question and discussion. An article prepared by the Committee's staff reports each lecture in the local press. A supply of short pamphlets is sent to the secretary of each group shortly after the speaker's visit.

No general, and indefensible, claim that cancer is curable is made. Speakers emphasize the very good results of early treatment of the accessible cancers in women. They describe "warning signs" (not "cancer signs"), which always require a doctor's advice: lump in the breast, unexpected bleeding, a sore that does not heal quickly. None of these signs can be imagined, and all require investigation whatever their origin. Speakers are at pains to avoid fear techniques. Since fear has not made people seek advice in the past, there is no reason to suppose they would do so if their fears were magnified.

Great attention is paid to the manner of addressing the public. In the present climate of fear surrounding cancer, how one talks about it is probably as important as what one says. Speakers are advised on the technique of lecturing and the use of bright visual aids to add interest and make learning easier. Every effort is made to take account of existing prejudices and mistaken beliefs and to bear in mind that people's fears and emotions are deeply involved in their thinking about cancer. All the information given is honest; but the more hopeful and largely unknown side of cancer treatment is given some of the publicity that is its due. Brief recorded interviews with cured patients are played during lectures—with considerably more effect than the recital of percentage survival rates.

The need for some form of education is obvious. Rather more than half of all cancer patients wait more than three months after seeing symptoms before seeking medical advice. Therapeutic methods therefore have a fair chance of success in less than half the cases. There is pathetically little confidence in the efficacy of treatment when cancer is so generally believed fatal. The failures of treatment provide their own unhappy publicity; the successes go unsung, because few know of what they were cured, and fewer are willing to talk about it. Whatever the eventual effects of early treatment on the five-year survival rates, it is axiomatic that the earlier any disease is treated, the better. The primary need is to promote confidence in the value of treatment and to get cancer talked about as just another disease. It is now beyond all doubt that a carefully conceived and executed programme of education neither causes cancerphobia, nor adds to the work of general practitioners. Any propaganda that does so is bad propaganda.

## REFERENCE

WAKEFIELD, J., and DAVISON, R. L. (1958) *Brit. med. J.*, i, 96.

**Dr. E. V. Kuenssberg:**

As a General Practitioner it has been brought home to me that patients are realists, particularly in the absence of pain. They consider their symptoms and signs in relation to the likely interference with their life and function and responsibilities. If an abnormality does not cause much discomfort the thought that there may be absence from work, with loss of earning, is more important to the patient than is usually realized.

Some of the principal points we have learnt as being of great importance in another field of medicine, namely tuberculosis, where early diagnosis and public education have also been a problem, are the following:

(1) Speed with which diagnosis can be made.

(2) Availability of treatment.

(3) Patients will not come forward even for diagnosis unless they know that some means of financial help will be available should they be found to be suffering from the "dreaded disease".

One of the most important lessons from this is that it is high time we paid more attention to speeding up the investigating or diagnostic proceedings. For instance the chest physician who has a day bed for his suspected lung cancer case, and who can do all his investigations,

X-ray, tomographs, bronchograph, bronchoscopy, including biopsy plus a general check-up that day, and have a consultation with the chest surgeon and radium or X-ray therapist that afternoon, can thus give the patient either a clean bill of health, or a programme for treatment including an approximate date for admission to hospital. This will do far more than the type of investigation which forces the patient to trail his increasing worries from hospital department to hospital department over several weeks.

The importance of giving the family doctor adequate diagnostic facilities must also be stressed.

In one particular field of cancer, early diagnosis may well be placed into the family doctor's hands. Professor R. Kellar of Edinburgh University, Department of Obstetrics and Gynæcology, has demonstrated that by inviting general practitioners to take cervical smears by the Ayre method, it is possible to detect early unsuspected cervical malignancy in approximately 15 per 1,000 women thus examined. This was done in collaboration with the College of General Practitioners, South-East Scotland Faculty, from where the full report will be published elsewhere. The cytological examination of the smears was carried out by Dr. A. F. Anderson and his co-workers at Edinburgh.

These cervical smears were taken during the ordinary consulting hours from:

(1) All women who presented themselves for post-natal examination.

(2) In women who had menopause problems, without histories necessarily pointing to any gynæcological disease.

(3) In women where a complete medical examination was indicated for one reason or another without again any obvious gynæcological complaint, or in women seeking advice on family planning.

The technique of taking cervical smears proved suitable for general practice and did not worry the patient and it has now become a valuable part of our diagnostic facilities which we would not like to be without.

Taking cervical smears is, of course, no substitute for a gynæcological opinion. It is a useful screening test of the clinically unsuspected women.

Data collected by my partners and myself show an impressive rate of positive smears for the women in the age groups of 30–40. If we can succeed in taking smears from the remaining women in our practice in those age groups we would take an important step towards early diagnosis of a malignant disease which has its full-blown clinical incidence at 45 years of age. The cost of not detecting early cancer or precancerous conditions is illustrated by the fact that of 4 women who were found during this survey in our practice with clinical signs of cancer, 2 are now dead, the remaining 2 having a poor prognosis, whilst the expectation of life of the eleven who have been discovered by means of cervical smears during the College of General Practitioners investigation must be considered infinitely better.

SUMMARY

(1) Speedy and decisive methods of diagnosis and treatment must be made generally available to gain the confidence of the patient and reduce the cruel, anxious time often at present associated with the diagnosis of cancer.

(2) Economic implications must be considered if patients are to come forward freely.

(3) The family doctor must be the fundamental guide in all diagnostic problems and be given everywhere good facilities for early diagnosis.

(4) The cervical smear method seems to be specially effective as a screening test when applied in General Practice.

(5) We cannot rely on mass education and propaganda alone, but must have an efficient and well-supported family doctor service.

**Mr. Linton Snaith:**

One of the problems involved in cancer propaganda was put to me very forcibly recently by a general practitioner friend of mine in the North-East of England. He pointed out that if a patient presented with disturbing symptoms, and he wished to make an appointment with a consultant he might have to wait two or three weeks and then after the appointment admission to hospital might be deferred for another three or four weeks. This seems to me to be a very relevant objection from the point of view of the general practitioner. If we are to achieve early diagnosis and treatment of cancer and offer the public such a service, one of our first essentials is the establishment of adequate out-patient consultations at hospital involving a delay of no more than a few days for making an appointment, and the provision of sufficient hospital beds for the immediate admission for investigation of any case presenting disturbing symptoms. We all know the difficulties, but it is no use urging the public to seek early advice if we are not in a position to furnish that advice immediately and to allay fears by immediate admission and investigation.

# Section of Surgery

President—A. DICKSON WRIGHT, M.S., F.R.C.S.

[*December* 4, 1957]

## TRANSATLANTIC DISCUSSION ON ADVANCES IN CHEMOTHERAPY OF CANCER[1]

*Moderator for the American Team:* **Dr. Leandro M. Tocantins** (Philadelphia).

*Moderator for the British Team:* **Mr. A. Dickson Wright** (London).

**Dr. Leandro M. Tocantins** (Philadelphia):

Ladies and gentlemen of the seen and unseen audience and our confrères overseas: Chemotherapy now occupies the centre of the stage in the treatment of cancer. The leukæmias and lymphomas, even though some doubt whether they are forms of cancer, are being widely treated with chemical compounds. Every year sees a slight but definite advance. This afternoon in this country (and it is snowing very badly here, Mr. Dickson Wright), and this evening in London, which I understand is a classical foggy evening—a London fog—we and our British colleagues discuss the chemotherapy of cancer with special attention to the leukæmias and the lymphomas.

Our two countries have contributed a great deal to the development of our knowledge of these diseases. We should like, at this time, to salute the memory of Thomas Hodgkin, the adventurous and shrewd clinical observer who, 125 years ago, described the disease that bears his name. British physicians from Hodgkin to Sir Lionel Whitby have added much to our knowledge of the leukæmias and lymphomas. More recently British workers, some of whom are members of your panel, have played and continue to play an important role in the development of the chemotherapy of these disorders. We are privileged to greet and express our appreciation to Professor Haddow, one of the world leaders in the field of cancer chemotherapy, to Dr. Wiltshaw of the Royal Marsden Hospital, to my good friend Dr. Bodley Scott of St. Bartholomew's Hospital, and to our fellow hæmatologist, Dr. John Wilkinson of Manchester. We are fortunate in enlisting the co-operation of the Section of Surgery of the Royal Society of Medicine.

**Mr. A. Dickson Wright** (London):

We are collected here on an extremely foggy night to deal with a subject which is to many of us a very foggy one. The pictures of your panel members are in front of us and we welcome this opportunity of discussion.

Chemotherapy at the moment seems to be the greatest hope in the treatment of cancer, and it is interesting that the diseases to which it has been first applied are those that were brought to light by Thomas Hodgkin in his paper published 125 years ago.

I would like to introduce our speakers: On the far right is Professor Haddow, Director of the Chester Beatty Institute, of whom you have already spoken. Next to him is Dr. Wiltshaw who worked for two years with one of your great cancer research workers, William C. Mahoney in Boston. On my left is your friend Dr. Bodley Scott, and on the extreme left Dr. Wilkinson, who is on the staff of the Infirmary at Manchester.

[1]Members of the American panel were attending the American Medical Association's Clinical Meeting in Philadelphia, Pennsylvania. The discussion took place at the suggestion of the American Medical Association. The transatlantic link was provided by courtesy of Messrs. Smith Kline & French Laboratories, Ltd. This account of the discussion is published by kind permission of the American Medical Association.

**Dr. Tocantins:** The first speaker will be Dr. Sidney Farber, Professor of Pathology at the Harvard Medical School.

**Dr. Sidney Farber** (Boston):

In making these introductory remarks I would like to recall that it is less than fourteen years since the temporary control of cancer in man was produced by the use of a chemical agent, thus giving realization to the hope that achievements in the chemical control of infectious disease might be paralleled in cancer. The last few years have witnessed temporary chemical control, characterized by improvement in health, often complete clinical remission, and increase in survival of patients with lymphoma, Hodgkin's disease, and both acute and chronic leukæmias. For many of these great advances we are indebted to our British colleagues, many of them working in association with Professor Haddow at the Chester Beatty Institute.

Under the term chemotherapy we will include alkylating agents such as the nitrogen mustards, antimetabolites such as folic acid and purine antagonists, a group of antibiotics and hormones, hormone analogues, and cortical steroids, and finally viruses, which I would choose to regard as chemical agents when they are effective against cancer, and bacterial products such as the bacterial polysaccharides. A wide variety of disseminated tumours in man, impossible to cure by other methods, has shown response to some of these agents, which have also been of value initially in the treatment of lymphoma and leukæmia.

What of the future? Solution of the problems of acquired resistance and of toxicity would increase greatly the effectiveness of those agents at present in use, and might well convert temporary control into permanent cure. A new era of combined radiotherapy and chemotherapy has been opened. The possibility of treating radio-resistant forms of chronic leukæmia, lymphoma, or Hodgkin's disease by chemical potentiation of radiotherapy is being studied. This study was initiated because of the profound effect of radiotherapy on some hitherto radio-insensitive tumours, such as the rhabdomyosarcoma, when combined with treatment with agents such as Actinomycin D.

Rational approaches to the synthesis of new chemical anti-cancer agents have been created, either by basic research or by knowledge acquired concerning the mechanism of action of carcinolytic agents of proved value. Most programmes are concerned with the synthesis of additional alkylating agents, or with the search for new antimetabolites, anti-enzymes or nucleic acid inhibitors.

These achievements of chemotherapy of cancer in man have led in the United States to the inauguration by Congressional action of the largest voluntary co-operative medical research programme ever attempted in peacetime. This programme, administered by the National Cancer Institute in Bethesda, unites the several private organizations and the branches of the Government with interests in this field, and includes communication with investigators in all countries. Greatly increased support to individual investigators, groups and institutions has been made available for basic as well as applied research. In addition, large co-operative programmes in the several areas of importance such as organic synthesis, screening, methodology, pharmacology, biochemistry, endocrinology, and clinical investigation have made possible rapid expansion in all areas. Of great importance is the large-scale participation of industry in this programme. An empirical programme administered by Dr. Kenneth Endicott of Bethesda is testing during this year over 45,000 chemicals and antibiotics . . . (*BREAK IN TRANSMISSION*) . . . against transplanted tumours in the mouse. Over one hundred clinical groups under Dr. Israel Ravdin of Philadelphia co-operate in a clinical study of chemical compounds in man. It is estimated that at least 4,000 analogues of known hormones have been synthesized by industry, which have not yet been studied clinically. From these various programmes, new antibiotics, hormone analogues, and chemicals will soon become available in considerable numbers, some possibly capable of exerting permanent control of lymphoma, Hodgkin's disease, and acute and chronic leukæmia. Such discoveries in this field would certainly be followed by application to the many other forms of disseminated cancer in man.

**Mr. Dickson Wright:** Dr. Wiltshaw will speak on the subject of when a chemotherapeutic agent can be considered a failure.

**Dr. Eve Wiltshaw** (London):

This apparently negative approach to therapy of malignant disease is presented because of its practical importance to all those people trying out new drugs in clinical practice. It now appears quite certain, not only from what Dr. Farber has said, but also from recent developments at the Chester Beatty Institute that the number of compounds being presented for clinical trial will outpace the material available on which adequate trials can be per-

formed. It is therefore of increasing importance to have some means of deciding at an early date whether it is worth while giving a substance a large-scale trial or not.

The first problem is one of specificity. I believe that Dr. Farber has the feeling that each substance should be tried against every kind of malignancy. This ideal is very difficult to achieve because of the large number of cases needed and the extreme rarity of some forms of tumours. Again, how many cases of each tumour should be given the compound to assess its efficacy, as one can hardly expect 100% success all the time?

The second problem is one of correct dosage. At first an empirical approach must be used to assess its side-effects—if these are serious the clinician feels more inclined to give up a drug early despite the fact that its efficacy may only be manifest when doses producing these effects are given.

If the original nitrogen mustard had been given up because of nausea and vomiting we should never have had the clinical benefit with which we are all familiar to-day. Nowadays, with the newer nitrogen mustards we tend to give them in amounts which do not cause nausea and vomiting.

The third problem is the comparison of one anti-tumour agent against another. The difficulties here are very great because of the variability in the natural history of malignant disease, and the unknown dosage equivalent of two drugs. So far, there are very few papers published comparing two chemotherapeutic agents objectively and this must be a development of the near future.

If a patient with carcinoma of the bronchus and multiple metastases responds to a compound, with regression of the tumour and freedom from symptoms and signs for eight months, then one can be fairly certain the anti-tumour agent is responsible and a great deal more work should be done on it. But if the answer is a negative one after trial on, say, 30 cases of various carcinomata, how far should one press the use of the substance for further trial?

**Dr. Tocantins:** One of the difficulties of the treatment of cancer with chemotherapeutic compounds is to make sure that the result that one obtains is due to the compound used. One begins, of course, with tests in the animals and subsequently applies the results to man. Dr. Sidney Farber said there is now in progress a vast programme of testing these compounds in the human lymphomas and leukæmias, and we have with us here Dr. Emil Frei, the head of the chemotherapy section of the National Cancer Institute who will tell us how to go about this in the right fashion.

**Dr. Emil Frei** (Bethesda, Maryland):

One of the major developments in cancer chemotherapy in the past year or two in the United States has been the establishment of group research, that is the co-operation of several clinical services in the investigation of anti-tumour agents. The orientation of these groups has varied somewhat, though, in general, they are endeavouring to apply the principles of the therapeutic trial which have proved so helpful in drug evaluation in infectious diseases, to cancer chemotherapy. As chairman of one of these chemotherapy groups, I would like to discuss some of the problems of such research.

The major criticism of this approach is that it is premature because the effectiveness of present drugs and potential new drugs is so limited that careful evaluations are unwarranted. In fact we have profoundly effective agents. One has only to observe the virtually complete disappearance of the acute leukæmic process, or the marked suppression of clinical and hormonal evidence of metastatic choriocarcinoma recently described by Dr. Hertz and associates, to appreciate the efficacy of currently used drugs. Such improvement is unfortunately only temporary. Nevertheless such agents certainly deserve careful study as methods of improving response. In this regard, it is important to point out that the marked anti-tumour activity of the folic acid antagonist in choriocarcinoma was achieved with a completely different dose schedule from that conventionally used and was not realized until ten years after these compounds became generally available. It is quite possible that we are far from realizing the maximum benefit achievable with some of our currently used chemotherapeutic agents.

A recurring criticism of the group approach is that, when the ultimate drug arrives for cancer, the question of its efficacy will be answered with a few patients. No elaborate study, no group approach will be required. This is of course true. What it does not say, however, is that the approach to such a drug may well be through the demonstration of a lesser degree of activity in a related compound. A "hole-in-one" is ideal, but infinitely more golf games are won with a putter. The cancer chemotherapist putter is basically the very well-designed—usually comparative—therapeutic trial, and his essential companions on the course are, among others, the statistician and the pharmacologist.

Of the many traps, the major one is the unpredictable natural history of cancer. We recently administered an experimental anti-tumour agent, 6-azauracil, to patients with

advanced, refractory acute leukæmia. 5 of the first 16 patients had some degree of hæmatological improvement. The details of these 5 cases were shown to clinicians both within and outside of our group and opinions ranged in the extreme, that is, everywhere, from the position that we definitely had an active compound, to the opinion that 6-azauracil was inactive. We clearly did not know how much spontaneous improvement may occur in advanced leukæmia nor how long after cessation of anti-metabolite therapy improvement may occur as a result of such therapy. In other words, in spite of a considerable expenditure of time and effort, the question we originally asked ourselves, does azauracil have anti-tumour activity in man, was unanswered. Not only did our driver not make a hole in one, but we are not quite sure in which direction the ball went. The pyrimidine analogues, of which azauracil is one, represent an important potential source of anti-tumour agents. The intensity of investigation in this area would be markedly influenced by an answer to the question, does azauracil or 5-fluorouracil have definite, even if limited, anti-tumour activity for man. For this reason our group is currently involved in a carefully designed comparative study of azauracil; that is, we picked up our precision instrument, the putter.

In summary, the cancer chemotherapy co-operative groups and the approach to chemotherapy that they represent constitute a major advance in methodology. Within a few years the place of chemical agents in the treatment of cancer should be much more clearly defined, and the evaluation of new agents should be at once more efficient, effective, and comprehensive.

**Dr. Tocantins:** There are many pitfalls in the evaluation of these compounds, and that may account for the slowness of the development of knowledge in this field.

**Professor Alexander Haddow** (London):

Dr. Frei has spoken of the design and execution of therapeutic trials. I would like to spend a few moments in considering design and execution in the experimental chemotherapy of animal tumours. The design of experiment is partly empirical and partly rational. On the empirical side, we are always curious to know the effects of all kinds of chemical agents on tumours, but in this country we are perhaps less enamoured than in yours of purely routine screening. I believe that the design of experiments must be flexible and selective in order to establish leads which can then be pursued more systematically. On the rational side we have had many leads from the study of experimental carcinogenesis. One example I might quote is the discovery of the carcinogenic action of the amino stilbenes, which, in part, led on many years later to the discovery of potential chemotherapeutic activity in the somewhat related styryl quinolines. Again on the rational side, I plead for the importance of a working hypothesis, no matter how faulty. One good example is the cross-linking hypothesis originally devised to explain the requirements for action in the alkylating agents, later shown to be unduly simplified, but nevertheless one which has proved tremendously fruitful in practice in leading to the discovery of new types of active agent. In other words I believe strongly that experimental chemotherapy should not be divorced from the fundamental programme. Each reacts on the others essentially.

As to execution, certainly it is desirable to test compounds on as wide a spectrum of tumours as is possible. But in practice this is not always easy and again it is necessary to be selective. In my own Institute many years ago we selected the Walker rat carcinoma among many others as a desirable initial test object for orientation purposes. It is not so sensitive as to be misleading, nor is it so resistant that it may hide the action of potentially interesting substances. Its use has set us on the trail of many leads, some of which have led to successful clinical application. Several agents are now known which will suppress the growth of this tumour completely. Compounds showing promising activity are then subjected to more strenuous tests: for example, on the growth of other transplantable tumours, spontaneous mammary cancer of mice and chemically induced sarcomata. In general these tend to be much more resistant. The small number of agents which still show some promise may be considered for clinical trial.

This brings me to the point of the extent to which the findings from animal experiment can be translated to man. Of course we know many which cannot be translated on account of undue toxicity and side-effects, the reason perhaps depending on differences in metabolism of these substances in different species. Nevertheless we have been impressed by the frequency with which animal findings can be applied direct to man, and good examples are seen in chlorambucil and Myleran. Clinical trial should be started with the utmost caution and subject throughout to the very highest critical standards. It may take a year or two to establish the details of dosage and the general pharmacology. When this is done, and prior to publication, we found great advantage in extending the trial to other centres. In conclusion, I would like to record our thanks to very many American friends who have done so much to help us in this direction, and especially to Dr. Sidney Farber.

**Mr. Dickson Wright:** I would like now to pass over to Dr. Tocantins for him to introduce his third speaker, Dr. Custer, who is going to speak on the relation of the histology of lymphoma and leukæmia to the aggressiveness of the process and its response to therapy.

**Dr. Tocantins:** Dr. Philip Custer, who is Associate Professor of Pathology at the University of Pennsylvania School of Medicine, has given a great deal of thought to the study of this particular point and he is now going to tell us his experience with it.

**Dr. Philip Custer** (Philadelphia):

As Dr. Frei has already emphasized, the natural behaviour of a given type of malignant tumour in a given individual is quite unpredictable. In no category of neoplastic disease does this hold so true as in the lymphoma-leukæmia complex, where even the untreated tumour may display vagaries including changes in its cellular composition.

It is traditional that the lymphomas and leukæmias are divisible by virtue of their predominant histologic structure, and various schemes of terminology have been applied, each with its merits and demerits. In this country the more usual catalogue of lymphomas designates the follicular or nodular form, the lymphocytic or lymphosarcomatous type, the reticulum cell or pleomorphic variety, and Hodgkin's disease, the last being subdivided into the so-called paragranuloma in which lymphocytes predominate, the granuloma with its multiplicity of cell types and inflammatory, necrotizing and desmoplastic aspects, and the sarcoma which resembles primary reticulum cell lymphoma. British pathologists seem to prefer the term "reticulosis" with appropriate adjectives to indicate this variety of patterns except for Hodgkin's disease, under which our subdivisions are unspecified. Leukæmias are classified as granulocytic, lymphocytic, monocytic, thrombocytic and plasmocytic, with gradients in differentiation of the cells which generally signify an acute or chronic course. Relationships with erythremia, erythremic myelosis, myeloma and myelofibrosis occasionally become apparent.

It is becoming accepted, however, that the cellular pattern of the lymphomas and leukæmias is not necessarily a static one, that transitions from one form to another do come about, and that a composite tumour made up of various derivatives of the reticulo-endothelial system, including fibroblasts and angioblasts, may evolve from an initially pure form of neoplastic cell growth.

As to the clinical manifestations of the malignant process in each category, whether pure, merging or mixed, we have found it quite impossible to predict the course of the disease, irrespective of treatment. Left to itself, the growth may pursue an indolent course for some years, perhaps with completely static periods or even spontaneous regressions, as one notes most frequently with follicular lymphoma, Hodgkin's paragranuloma, and chronic lymphocytic and granulocytic leukæmia. Yet at some unpredictable time any one of these relatively benign processes may explode into a rapidly fatal phase. In a comparable group of patients in whom the microscopic appearances of the malignant tissue are identical, however, there may be an extremely aggressive growth surge almost from the very outset.

This capricious behaviour likewise applies to the responsiveness of these tumours to treatment. Malignant tissue in one person may melt away almost miraculously following administration of a few milligrams of nitrogen mustard or one of its analogues, but a histologically identical tumour in the next patient may remain relatively untouched by the same agent in like dosage. Furthermore, a lymphoma quickly destroyed by a cancerocidal compound may return to plague the patient in a few weeks, while the same spectacular disappearance of precisely the same type of tumour in another person may be long-lasting. Again, an initially stubborn tumour which requires repeated treatment of one sort or another at the outset may recede and remain quiescent for years without further concern.

Individual sensitivity to the administration of cancerocidal agents is not confined to neoplastic tissue. There is a rather wide scatter in the amount of these drugs that patients can tolerate before bringing about serious depression of the bone-marrow and consequent cytopenias in the peripheral blood. All too often the enthusiastic chemotherapist will destroy the patient along with the malignant disease by virtue of an empty bone-marrow. It is of extreme importance, then, that every patient be regarded as an individual experiment in connexion with the administration of any cancerocidal agent, be it conventional or new.

All of this points to the human as the poorest of experimental animals, particularly the sick human, who is in no sense comparable to highly inbred strains of tumour-bearing animals on whom the new chemotherapeutic materials are tried initially. Thus, the first clinical trial of a substance which has shown promise in animal experimentation may prove very discouraging, for it must be used with patients who have failed to respond to conventional treatment. While most of them die, the study of their tissues at autopsy none the less offers an important means of evaluating the relative toxicity of the chemical on both

neoplastic and normal cells, especially the blood-forming ones which are generally the most sensitive. The final phase, and the one requiring the greatest courage on the part of the investigator, is the testing of a promising cancerocidal agent on patients whose malignant disease is not overwhelming and who could probably be salvaged by conventional forms of treatment. Here, too, one is handicapped in his evaluation by the individual variants already recounted.

In an effort toward better understanding of the variables in humans, we have planned experiments which might disclose differences in host resistance to the tumour or in antigenic capacity of tumour tissue. By some such means it might prove possible to weight the results of clinical chemotherapy of cancer.

**Dr. R. Bodley Scott** (London):

I would like to continue the theme which Dr. Custer has started. I think that in this connexion it is important to divide lymphomas from leukæmias because there is a considerable difference between the two in the relation between histological appearances and response to treatment and the aggressiveness of the tumour. So far as the lymphomas are concerned, there is remarkably little correlation between the histological picture and the aggressiveness of the disease.

Dr. Custer's remarks also open up the complicated question of the classification of these diseases, and this is as confused as was the classification of nephritis twenty-five years ago. Dr. Custer has offered a classification which probably would not be acceptable to most clinicians or pathologists in this country. Many of us do not believe in three different kinds of Hodgkin's disease, one of which may turn into the other; we believe that the histological pattern remains essentially constant, and that one disease does not turn into another in the way that has been recorded. If these different histological patterns indicate different diseases, do they show a different response to different chemotherapeutic agents? The answer so far as the lymphomas are concerned is yes. For example, most people would agree that the original nitrogen mustard, $HN_2$, is much more effective in Hodgkin's disease than are other drugs such as chlorambucil or the polyethyleneimines. On the other hand it is the usual experience that chlorambucil and the polyethyleneimines are more effective in the diseases in which the main feature is lymphoid hyperplasia—lymphatic leukæmia, lymphosarcoma, and lymphoid follicular reticulosis or follicular lymphoblastoma. It may be that the original nitrogen mustard is more effective against reticulum cell proliferation, and the other drugs against lymphoid cell proliferation.

When it comes to leukæmia, it seems to me that the situation is a good deal clearer. There is undoubtedly a relationship between cytology and aggressiveness in chronic myeloid leukæmia. For instance, at one extreme there is the rare neutrophil leukæmia which goes smouldering on for perhaps ten years; in the middle there is the common chronic myeloid leukæmia in which the average duration is perhaps three or four years, and this will usually terminate by a sudden outpouring of primitive myeloblasts.

There is also a clear-cut relationship between the response of the diseases to chemotherapeutic agents. For instance, chronic myeloid leukæmia will respond by some degree of remission to almost all chemotherapeutic agents, but when it reaches the undifferentiated myeloblastic stage it only responds to 6-mercaptopurine. In chronic lymphatic leukæmia, the small cell type is generally admitted to run a more chronic course than the large cell type, although there are many exceptions. Finally in the acute leukæmias there is possibly some relation between cytological type and the response to chemotherapeutic agents. When there is general agreement that a case is one of myeloblastic or lymphoblastic leukæmia, there is a good chance that remission will occur with 6-mercaptopurine. Remission is much less likely when it is one of those cases where nobody can agree on the exact nature of the cell and when one hæmatologist says it is a myeloblast, the next a lymphoblast, and the third a monoblast. That is to say, where the cells are completely undifferentiated, the chances of remission are far less good.

**Dr. Tocantins:** We must look for the answer to the rationale of chemotherapy, principally to the man who is doing fundamental experimental work. We have with us here this afternoon one of the leading exponents, Dr. Howard Skipper, who is Director of the Southern Research Institute and Professor of Experimental Pathology, University of Alabama Medical School

**Dr. Howard Skipper** (Birmingham, Alabama):

As a Southerner, I am particularly honoured to be asked to join this transatlantic conference. As our friends in England may remember, there was a bit of a strife in this country between the North and the South almost a century ago. We, in the South, did not really lose this war; we simply wore ourselves out winning battles. This conference is an excellent demonstration of the absence of provincialism or nationalism in medical science.

I was asked to discuss a topic on which there is no general agreement, no hard core of

accepted facts—just opinions and the belief that if there were at hand *a sound rationale* for direction of research in the area of cancer chemotherapy, the whole world-wide effort would proceed in a more orderly, efficient, and rapid manner. Therefore, in the absence of any real over-all rationale for cancer chemotherapy, you must listen to some vague "semi-rationales", or something allied thereto.

The biologic entities most generally associated with the cellular change resulting in cancer are genes and viruses. We know that both genes and viruses are nucleoprotein in nature and that the hereditary capacity of genes and viruses is contained in their nucleic acids. Thus, on a biochemical basis, cancer might appear to be a lesion in cellular nucleoprotein possibly resulting in a deleted or inactivated anabolic or catabolic enzyme responsible for some rate-controlling biochemical events. Here I have covered, or attempted to cover, a considerable ignorance with big words, but I have also tried to suggest a general concept which would allow some correlation between the somatic mutation and virus ætiology concepts (a virus-like particle is structurally well suited to causing genic changes in a cell). Also the concept that gene changes are associated with cancer is well suited to the enzyme-deletion concept which appeals to me. From the theoretical standpoint, it seems possible that rates of normal cell growth and division may be associated with a balance between certain anabolic and catabolic reactions, and deletion of catabolic catalysts (resulting from gene changes) might well shift the balance to a state of uncontrolled net synthesis and cell growth and division.

The agents which affect the course of leukæmia in animals and man, by and large, are agents which affect nucleotide and nucleic acid metabolism. X-radiation, a long-employed method for treatment of certain leukæmias and many other neoplasms, is an inhibitor of nucleic acid synthesis. Urethane, an antileukæmic agent discovered by Professor Haddow and his associates, affects glutamine and pyrimidine metabolism. Azaserine and DON, glutamine antagonists discovered by the Sloan-Kettering and the Parke, Davis groups, are inhibitors of purine nucleotide synthesis. A-methopterin, a useful temporary anti-leukæmic agent discovered by Dr. Farber and his group, blocks purine nucleotide and nucleic acid thymine synthesis. 6-mercaptopurine which came from collaborative work between the Burroughs Wellcome and Sloan-Kettering Institute laboratories and which causes temporary regressions in some cases of human leukæmia, is almost certainly a purine nucleotide antagonist. Work in both Professor Haddow's laboratory and ours has shown that nitrogen mustards do indeed alkylate nucleic acids.

Thus, generally speaking, it appears that the antileukæmic agents in use to-day probably act as inhibitors of nucleotide metabolism (affecting co-factor or nucleic acid synthesis) and, in turn, inhibit cell division. Therefore, one rational approach to cancer chemotherapy might be synthesis of a wide variety of analogues of the cellular intermediates *en route* to co-factor nucleic acid moieties. I can think of a great number of compounds that could be synthesized for trial on this semi-rational basis. Many of these, I am certain, are being made to-day in laboratories throughout the world.

A second and perhaps more long-term rational approach is the direct search for the biochemical lesions responsible for cancer. If I were in possession of a genie with the power to grant one wish, I would, of course, ask the structure of a compound which would cure all cancer in man, but if this genie was a specialist who did not go along with applied research (a real fundamental genie who gave answers only to fundamental questions), then I would ask him what are the exact basic biochemical changes responsible for alteration of a normal cell to a cancer cell. I would publish this knowledge immediately (giving proper credit) and hope that such knowledge would make possible a direct scientific approach to the problem of (1) action which might be taken to prevent such chemical events in man, or (2) the design of drugs which would exploit these biochemical differences and provide the cytotoxic specificity required for curative cancer chemotherapeutic agents.

Still another rational approach to advancement of the status of cancer chemotherapy is that of unravelling the cause of failure of our presently known temporary antileukæmic agents. Development of drug-resistant population of neoplastic cells is possibly one stumbling block *en route* to our goal. The basic knowledge required for some understanding and rational planning on the problem of drug resistance is being acquired more rapidly than many of us realize. It may be hoped that the possession of such knowledge will make it possible to devise means for coping with the development of drug resistance associated with present clinical chemotherapy of the leukæmias.

Finally, there are two general rational approaches to the advancement of cancer chemotherapy: (1) a search for the basic lesion of neoplasia on the biochemical level with hopes that such knowledge will allow for selection or design of drugs with greater usefulness, and (2) continued design and trial of drugs on the best hypotheses at hand hoping that better drugs will turn up and that study of their modes of selective action will lead us to the basic biochemical lesions of cancer. I personally encourage and endorse efforts in both directions.

**Dr. Tocantins:** The study of drug resistance and of the mechanism of action of the chemotherapy of leukæmias and lymphomas leads almost into the heart of the mechanism of life. In attempting to control cancer we are going to learn a great deal about the mechanisms of life itself, underlining Dr. Ewing's statement that the study of cancer was virtually the study of life.

**Mr. Dickson Wright:** Professor Haddow will now speak upon the prospects of cancer chemotherapy.

**Professor Haddow:**

Cancer chemotherapy is obviously still in an embryonic stage. Nevertheless a good deal of progress has been made in the past ten years, resulting in agents which are clinically useful, even if only in a very limited sense. This progress still continues with experimental emphasis on agents with a far higher therapeutic index than those so far used. The present lines of work must be extended, and it would be quite wrong to discount the possibility of discovering new agents of greatly enhanced activity and wider application. But having said this, I am doubtful whether purely cytostatic agents or the antimetabolites, as we know them, have any permanent place in treatment. I have already made the point that the study of experimental chemotherapy should not be divorced from fundamental studies, and I believe the main importance of all these agents lies not in their practical application but in the light they shed on mechanisms of action, and on the nature of the cancer cell itself. As one example, many of the alkylating agents are capable of carcinogenic action in animals and much has been learned of the ways in which they could combine in the cell, with nucleoprotein perhaps in particular, to bring this about. The tentative conclusion, although not by any means proved, is that such agents bring about malignant change through a process of cytogenetical loss. The biochemical nature of the loss is not so far known. We have, however, speculated along the lines just referred to by Dr. Skipper whether it might involve the elimination of enzyme systems responsible for regulating the growth of the normal cell, so liberating the synthesis of growth-promoting substrates. This would account for the continuous and unregulated growth of the cancer cell. This idea is not only attractive but in very many ways reasonable. If it were to prove sound, we might perhaps envisage a new kind of chemotherapy in the future, in which the growth-regulatory functions, apparently deficient in the cancer cell, would be re-imposed. This recalls certain types of substitution-therapy we already employ elsewhere, especially in pernicious anæmia, much of the underlying pathology of which is reminiscent of certain aspects of malignant change.

To summarize, progress will be made on present lines, we never know with what surprises, but the same agents will also be used to study the mechanism of carcinogenesis and to establish the essential biochemical differences between normal and cancer cells. This could lead to a new form of chemotherapy based upon rational understanding, and very different in kind from that which we employ to-day.

**Dr. Tocantins:** We are very fortunate this afternoon in having two of the leading exponents of the chemotherapy of leukæmia in this country, Dr. Farber and Dr. Burchenal. Both of these men have made very vigorous attacks on the leukæmia problem, and I take great pleasure in introducing Dr. Joseph Burchenal, Professor of Medicine, Cornell University Medical College, who will speak on the practical clinical results that can be obtained by chemotherapy of the leukæmias.

**Dr. Joseph Burchenal** (New York):

There are three classes of agents at present available for the treatment of acute leukæmia. First there are the folic acid antagonists discovered by Dr. Farber's group, of which Methotrexate, previously called amethopterin, is perhaps the best. Secondly, there are the purine antagonists exemplified by mercaptopurine, chloropurine and thioguanine. None of the latter is any better than 6-mercaptopurine. Thirdly we have the adrenal steroids. Of the last the prednisone type is preferable since there are less of the undesirable side-effects of sodium and water retention. The folic acid antagonists and purine antagonists require three to eight weeks to exert their beneficial effects, but the remissions are generally longer than with the more rapidly acting steroids. For that reason we believe that the folic acid antagonists and the purine antagonists should be the main chemotherapeutic agents, and that the steroids should be reserved for emergency situations such as fulminating disease or gross hæmorrhagic tendency, where rapid action is essential, or for cases in which resistance to the antimetabolites has developed. In the acute leukæmias, signs and symptoms of meningeal infiltration occasionally develop. This may be treated successfully by intrathecal injections of Methotrexate or by radiation to the whole cranium. Beneficial effects have been achieved by intrathecal Methotrexate both in patients whose peripheral disease was resistant as well as in those whose disease was sensitive to Methotrexate.

Acute leukæmia in children may respond to all three types of therapy and a high percentage of patients will respond to at least one.

With such a regime as I have outlined we have found 50% of our last 253 children with acute leukæmia survived for just over twelve months as compared with the usual 50% survival of four to five months before these specific modes of therapy were available. Previously untreated adults rarely respond to the folic acid antagonist, but about 15–25% will respond to the purine antagonist and about the same response may be expected from the steroids. In patients who have responded at first to 6-mercaptopurine and have then developed resistance, Ellison showed that there is a 30% remission rate with Methotrexate so that it is important not to abandon folic acid antagonists in the acute leukæmias of adults. They should be tried after mercaptopurine has been tried. Since the percentage of adults responding to any therapy is small, the overall increase in survival time is not very significant, but in those in whom remissions are achieved, a median survival time of about twelve months can be expected.

In chronic granulocytic leukæmia, Myleran is the chemotherapeutic agent of choice. How survivals will compare over a long term with those after X-ray therapy is impossible to state for certain at this time. Preliminary studies by Krakoff *et al.* suggest that chlorambucil will also produce remissions in this disease.

In chronic lymphocytic leukæmia, chlorambucil is the drug of choice, but X-ray therapy to nodes and spleen is also excellent treatment. Preliminary studies by Galton and by our group have shown that Myleran can also produce remissions in this disease, but how it will compare with chlorambucil cannot at present be stated.

The adrenal steroids are of considerable value in controlling the hæmolytic anæmia and thrombocytopenia associated with this form of leukæmia, but again it is too early to assess the effects on survival time.

In the localized lymphomas we prefer localized radiation therapy. When the process is generalized, chemotherapy is indicated. For rapid effect in Hodgkin's disease, we prefer intravenous nitrogen mustard, or possibly intravenous T.E.M. (triethanomelamine). For maintenance therapy chlorambucil by mouth seems to be well tolerated and well absorbed. The adrenal steroids will produce regressions in lymphosarcoma and reticulum cell sarcoma, and are frequently beneficial in treating the hæmolytic anæmias associated occasionally with all the lymphomas.

The effects of these forms of therapy on the overall median survival time of patients with lymphomas is not at present clear, but it is our clinical impression that in certain cases marked increase in expected survival time can be achieved.

**Mr. Dickson Wright:** Dr. John Wilkinson will speak on practical clinical results.

**Dr. John F. Wilkinson** (Manchester):

I propose selecting from my series of 900 cases of leukæmia that I have treated with chemotherapeutic agents since 1942 when I first introduced the trichlorethylamine hydrochloride for intravenous use. I am interested that a number of speakers are coming round to my view that the most effective preparation in many of the chronic leukæmias is intravenous trichlorethylamine hydrochloride, and that the newer preparations are not so good although perhaps a little more gentle with the patients in that they do not produce as much nausea.

In the acute leukæmias there are very few agents that can produce prolonged and beneficial effects. With the nucleotoxic agents and the antimetabolites that previous speakers have mentioned such as aminopterin, amethopterin and 6-mercaptopurine, we have only been getting approximately 30% remissions for periods up to twelve to eighteen months. It is easy to get toxic effects if you are not careful, and the subsequent relapses are not easy to treat.

Our best results have been obtained with the steroid hormones, particularly prednisolone, and by giving prednisolone in high dosage and for prolonged periods we do get approximately 40% remissions for much longer periods. The first patient I treated was in 1951, and she only required treatment for six months. She had two courses of treatment in that period, and for six years has been perfectly fit and well without any symptoms. The blood is normal, the marrow is normal. Clinically she is a perfectly well child, back at school and leading a normal life.

We have tended to give up the anti-folic acid agents and concentrate on the steroids. It is interesting that children respond much better than adults in these acute leukæmias with one exception—the acute monocytic leukæmias appear to respond better in adults, some of whom we have been able to keep going for one to two years.

The chronic leukæmias do not benefit from the steroids nor from the antimetabolites, except that a few chronic myeloid leukæmias may respond to mercaptopurine. Both chronic myeloid and chronic lymphatic leukæmias respond extremely well and rapidly to intravenous trichlorethylamine hydrochloride. It may only be necessary to give two or three doses of 5–6 mg. intravenously, and large glands, the spleen and the liver will go down in a matter of a week or a fortnight. Of a series of 140 severe cases selected because they had large glands, spleens and livers, in the course of one to four weeks 94% lost their splenomegaly, and 91% their enlarged glands, the white cells returning to normal. They needed subsequent similar short courses of treatment at intervals varying from three months to over two years. One or two of these patients whom I first treated during the war are still alive.

The chemotherapeutic agents that we give orally have also introduced interesting possibilities. Chronic myeloid leukæmia responds very well to Myleran. One can ultimately reduce the dose in many cases to 2 mg. once a week, and with perhaps an occasional slight increase. Colcemid, (deacetyl-methyl-colchicine) acts similarly, but is not quite so easy to control. Chlorambucil has been disappointing in the myeloid leukæmias.

T.E.M. is a very dangerous drug, and, although it may be efficient for a short time, aplastic anæmia, thrombocytopenia, and agranulocytosis are frequent complications. I think T.E.M. should be removed from our armamentarium, particularly as we have better and safer therapeutic agents.

The chronic lymphatic leukæmias do not usually respond to Myleran, Colcemid, T.E.M., and Urethane, but they may respond to chlorambucil or to the substance R 48. If the patient has suitable veins the quickest and best treatment is either intravenous nitrogen mustard or intramuscular thioTEPA. Hodgkin's disease reacts similarly, and I know of no treatment as good as intravenous trichlorethylamine hydrochloride given in small dosages. In 80 cases of Hodgkin's disease, all selected because they had large glands that could be photographed and with large spleens, with doses of 6–30 mg. spread over two to three days, there was complete regression of the splenomegaly in 76% and partial regression in 16%, whereas in the lymphadenopathies 83% lost their large spleens and 9% showed regression. The survival time of these patients has been good, the longest to date being twelve years. None of these cases were of the mild type that often does not need treatment. In the other reticulosis, the results are not so good.

**Dr. Tocantins:** I regret that we are running a little behind our time because much of what Dr. Wilkinson said would I am sure be challenged by certain members of our panel. I would like to state that these proceedings are being broadcast and are being heard now in the National Cancer Institute in Bethesda, Maryland, and at the Walter Reed Army Medical Centre. We are even getting questions relayed to us from these two audiences.

The next few minutes will be dedicated to the questions from our panel to the British panel. The first question, which is being asked from Dr. Burchenal, is directed to Dr. Bodley Scott. Have you any experience with chlorambucil in the treatment of chronic granulocytic leukæmia or Myleran in chronic lymphocytic leukæmia?

**Dr. Bodley Scott:**

I have had no experience but I would suggest that the question be referred to Dr. Wiltshaw who I believe has some experience of Myleran in treating chronic lymphocytic leukæmia.

**Dr. Wiltshaw:**

Dr. Galton has treated 3 cases of chronic lymphatic leukæmia with Myleran, and he felt that in these cases he got a definite drop in the white cell count, and a response which could be expected with any of the other drugs, the only disturbing feature was that one of the cases got what he thought was disproportionate platelet drop and one case developed purpura. Of these cases, 2 of them were treated with 4 to 6 mg. daily and 1 case was treated in the early days of Myleran with large doses, in five days she received 318 mg. This patient had no purpura and proceeded to a remission of about two years. We think it worth while to use this drug in chronic lymphatic leukæmia.

**Mr. Dickson Wright:** Professor Haddow has given me a question for Dr. Frei. "Is there any evidence for the effectiveness of chemotherapy in delaying or preventing metastasis?"

**Dr. Frei:**

In choriocarcinoma, all of the patients treated had extensive metastases. There are studies currently in progress to determine whether chemotherapeutic agents, particularly alkylating agents, given at the time of surgery for the primary lesion, will prevent the subsequent development of metastases.

**Dr. Tocantins:** I would like Dr. Farber to answer some of the points that were brought up by Dr. Wilkinson, especially the giving up of folic acid antagonists in the treatment of leukæmia. Dr. Farber is the leading exponent of this treatment.

**Dr. Farber:**

May I combine my answer with the question of survival in some 900 children with acute leukæmia treated with folic acid antagonist, 6-mercaptopurine, and the corticosteroids during the past eleven years.

We have 50% survival fourteen months after the beginning of treatment; this includes all children whether they died within an hour after admission, or whether they had treatment or not. 10% are still alive at two and a half years; a few are still alive at four to four and a half years. One child had an unbroken folic acid antagonist remission of eighty-eight months—seven years and four months—and died, I am unhappy to say, a few weeks ago with staphylococcus infection, ninety-eight months after the beginning of therapy. It is not a question of which one of these agents is the best. In the course of treatment we need every one of them, and there is no question from our experience that folic acid antagonists may be given safely without the production of toxic effects and be productive of very long remissions. This is also the experience of Dr. Burchenal and many other people in this country. So that answer to the question is that all four of these agents, the corticosteroids, ACTH, folic acid antagonists and purine antagonists, have a very important place in the course of treatment of any given patient with acute leukæmia.

**Dr. Tocantins:** We have a question from Dr. Farber directed to Professor Haddow. "Do you consider it worth while to fashion experimental chemotherapy against lymphoma and leukæmia on the assumption that these disorders may be caused by a transmissible virus or agent?"

**Professor Haddow:**

I think your question indicates what I have already tried to stress, namely the great importance of fundamental studies on causation, including causation by viruses, and I think it is from these that new leads in chemotherapy will probably come. But I doubt if we are yet in any position to fashion agents against lymphoma or leukæmia on the assumption that these may be caused by some transmissible substance.

**Mr. Dickson Wright:** I would like to direct a question to Dr. Philip Custer from Dr. Wiltshaw, "What is the most effective agent in the treatment of myelomatosis?"

**Dr. Custer:**

So far Urethane has been our anchor to windward with myelomatosis. We have obtained good palliation in an appreciable number of patients. The majority, however, have not had any great prolongation of life, with the exception of one patient who is now in her fifth year of the disease under constant Urethane control.

**Dr. Tocantins:** I have a question from Dr. Farber to Dr. Bodley Scott. "What are your expectations in the treatment of the lymphomas from still greater super-voltage radiotherapy?"

**Dr. Bodley Scott:**

What one should expect from super-voltage radiotherapy is perhaps that a greater dose can be given to tumours, particularly deep tumours, with less damage to the skin and to the surrounding tissues. Therefore super-voltage therapy has a limited usefulness in lymphomata, particularly where the main mass is in the mediastinum or in the vertebral column causing pressure on the cord. Radiotherapy is never more than symptomatic in the treatment of these diseases because the diseases are potentially generalized from the beginning. I do not believe we can expect very much more from greater super-voltage radiotherapy than we already have from present super-voltage radiotherapy.

**Mr. Dickson Wright:** I would like to ask a question from Dr. Wiltshaw to Dr. Frei. "What is the place of chemotherapy in the treatment of the lipoid storage diseases?"

**Dr. Frei:**

That is a difficult question. The lipoid storage diseases in many respects resemble primary proliferative disorders. For this reason various anti-tumour agents have been administered to such patients. Evaluation is difficult because the natural history and interrelationships of some of these diseases are poorly defined. I know of no clear evidence that chemotherapy is beneficial in the lipoid storage diseases with the exception of hypersplenism which, of course, can develop and complicate any variety of lipoid storage disease. Under these circumstances adrenocortical steroids or ACTH are frequently helpful.

**Dr. Tocantins:** I have a question here which was sent from the National Institute of Health directed to Dr. Burchenal. "What is the best dosage schedule for Methotrexate in acute leukæmia?"

**Dr. Burchenal:**

I am not sure that anyone knows the best dosage. Not nearly enough work has been done clinically with differing dose regimes. The dose we generally use in a child, say of 5 years of age or slightly under, is 2½ mg. once a day by mouth. If that produces no effect after a time it may be necessary to go to 5 mg. daily, with the 2½ mg. daily we rarely see toxic manifestations and we can usually get remissions without toxicity.

**Mr. Dickson Wright:** A question from Dr. Bodley Scott to Dr. Skipper. "Is combined therapy by a number of agents at once of value?"

**Dr. Skipper:**

I can only speak of the effect of combination chemotherapy in experimental animals. I should like to make one brief statement on that point and then pass to Dr. Burchenal who has carried out combination chemotherapy in the clinic. I think that this is a theoretically very promising approach to the advancement of the status of cancer chemotherapy for two reasons. Theoretically, it is a good means for preventing the development of drug resistance, and also a method for obtaining sequential blockade in a series of chemical events which might result in potentiation. Certainly, unequivocal potentiation of the antileukæmic activity of drugs has been observed with combinations of drugs in experimental leukæmias and tumours.

**Dr. Burchenal:**

6-mercaptopurine and azaserine in mouse leukæmia and in sarcoma 180 have a definite potentiating effect. For that reason the combination of 6-mercaptopurine and azaserine has been tried in children with acute leukæmia. This study has been done by some 14 different co-operating groups and is still in progress. It appears that in a small percentage of patients the length of remission on 6-mercaptopurine can be prolonged by the addition of azaserine. I think that combination chemotherapy has a great future. All we need are some good compounds to use in combination.

**Dr. Tocantins:** We now have only about a minute or so to go, and there is one basic question that Dr. Skipper would like to direct to Professor Haddow. "Is enough effort being directed towards the discovery of biochemical differences between normal and neoplastic cells?"

**Professor Haddow:**

I think that insufficient work is being done along these lines. But much more has been done during the past ten years than ever before. Of all the rational approaches, this is by far the most important, and in saying this I am thinking not only of biochemical differences but also of biophysical and immunological differences between normal and cancer cells.

**Dr. Tocantins:** I should like to say how much pleasure we have had in this conversation with our British colleagues, and I am sure that for most of us here it has been very educational to hear what is thought on these matters overseas. What has struck us particularly is the agreement that exists between us. There have been disagreements, of course, and those could be probably exploited a little more, but what impressed me is the amount of agreement. I should like to convey to our British colleagues and to the co-ordinators our thanks for making this interchange possible.

**Mr. Dickson Wright:** Goodbye Dr. Tocantins and your colleagues, and thank you very much for the really splendid way you have covered the subject. I have written down here 26 different chemotherapeutic agents that have been mentioned during the course of this discussion and 12 different diseases. That gives an impression of the complexity of the subject, but I feel we have all gained a great deal from it and we are very grateful to Messrs. Smith Kline and French Laboratories, Ltd. for making this possible.

# Section of Dermatology

President—JOHN T. INGRAM, M.D., F.R.C.P.

[*January* 16, 1958]

**Psoriasis.**—D. I. WILLIAMS, F.R.C.P.

D. S., aged 41, housewife.

*History.*—This patient has suffered from psoriasis since the age of 5 years. For most of the time it has not been severe and has been readily controlled by treatment although never completely removed. At its best the lesions are confined to the legs only. In January 1957, she had influenza followed by a generalized flare of the psoriasis. She attended King's College Hospital for the first time at the end of March when she was suffering from a generalized scaling eruption, considerable pigmentation and pallor. The nails were thickened and discoloured. The lymph glands in the axillæ were enlarged. As she refused admission to hospital she was treated as an outpatient, with very limited success.

In July 1957 she consented to come into hospital on account of the generalized psoriatic erythroderma. At that time no other clinical abnormality was found. She was treated with prednisone, 15 mg. t.d.s. with some improvement. Reduction of the dose of this drug to 5 mg. t.d.s. was followed by relapse. For domestic reasons she left hospital early in October with the condition still extremely unsatisfactory. Further outpatient treatment did nothing to restore the condition. She was readmitted in the middle of November, still with an exfoliative erythroderma and generalized pigmentation with a suggestion of reticulation of the pigmentation, particularly around the neck. This time the liver was felt to be enlarged, three fingerbreadths below the costal margin. At the end of a month she had developed large numbers of macerated hyperkeratotic papules on the wrists and on the lower third of the legs. She left hospital just before Christmas and continues to attend as an outpatient.

*Past history.*—Non-contributory.

*Family history.*—No psoriasis.

*On examination.*—Generalized pigmentation, reticulate around the neck, with some telangiectasia. The trunk and limbs are covered with aggregates of dusky, small, slightly scaly papules, leaving tiny islands of apparently normal skin. There is considerable scaling of the lower third of the legs; the nails are thickened, discoloured and distorted. The liver is palpable three fingerbreadths below the costal margin. There is axillary adenopathy.

*Investigations.*—Biopsy of skin (2.12.57): "Section shows some hyperkeratosis and parakeratosis. There is a moderate acanthosis with elongation of the rete pegs. The papillæ are correspondingly elongated with a slight tendency towards clubbing at their apices. The upper part of the corium is diffusely infiltrated by a mixed cellular inflammatory exudate consisting of numerous reticulo-endothelial cells, and moderate numbers of lymphocytes and polymorphonuclear leucocytes. The histological picture is that of psoriasis." (Dr. M. E. A. Powell.)

White cell count persistently normal. Hæmoglobin 70–84%. Electrophoretic pattern: no significant change. Blood urea, serum proteins, liver function tests and chest X-ray were all normal.

*Comment.*—Members are probably wondering why I labelled this case "psoriasis". If I had not called it "psoriasis" I think I should have got lost in a vast waste of dermatological terminology. Certainly I was told she had had psoriasis since the age of 5 and one could suspect on looking at her, particularly at her arms, that there are remnants of psoriasis but at the time I saw her the condition had changed considerably and I felt that something nasty was happening. By the time I saw her she had pigmented considerably, there was a suggestion of reticulation and perhaps a little telangiectasia. I do not think there was any real atrophy and since that time she has developed all over the trunk a large number of dusky papules of a rather violaceous tint. The liver is now easily palpable, I do not know whether this is significant; so many people with exfoliative dermatitis get large livers. My feeling is

that this woman will ultimately develop one or other of the reticuloses. I thought it was interesting in view of the discussion we had last year concerning psoriasis, and the possible development of mycosis fungoides (*Proc. R. Soc. Med*, **50**, 771, 931). A few weeks ago Professor Degos told me of a number of cases of psoriasis at the St. Louis Hospital in Paris which had developed mycosis fungoides.

**Dr. A. Jarrett:** I thought this was a case of psoriasis that had developed into an exfoliative erythrodermia. I agree with Dr. Williams that the enlarged lymph glands would probably show the histological features of lipomelanic reticulosis, but I do not think that she will inevitably progress to a malignant reticulosis; in fact I think the chances are she will not. In a series of 16 cases of lipomelanic reticulosis followed over several years (3 of them to autopsy), none developed a malignant reticulosis.

**Dr. I. B. Sneddon:** I recall a case which was thought to be psoriasis for ten years and which then developed exfoliative dermatitis. After eighteen months in hospital small doses of superficial X-ray therapy entirely cleared the exfoliative dermatitis. A year later, typical tumours of mycosis fungoides appeared and the disease ended fatally. I agree with Dr. Williams that such a course may happen here.

**Dr. F. F. Hellier:** One has seen cases before in which a dermatosis which has been apparently psoriasis or some other skin condition changed into a reticulosis. Is this just the evolution of the disease or is the reticulosis a new development *caused* by the original dermatosis? If glands from widespread dermatoses are examined they show a reaction to irritation; chronic irritation anywhere may at times produce new growths. May it not be that the prolonged irritation of a chronic skin disease may lead to malignant changes in the skin which show themselves as a reticulosis?

**Dr. Grant Peterkin:** The dramatic response to X-ray therapy of the patient in Sheffield makes it look as if he was in the premycosis group. I would call this case psoriasis and premycotic eruption. Psoriasis is a common disease and we must expect that patients with psoriasis may acquire reticulosis which might not be related.

**The President:** When a case of psoriasis ultimately presents with mycosis fungoides I feel that it is coincidental. This psoriasis started at 10 or 12. The present eruption, like the parapsoriasis lichenoides, is of recent origin. I wondered if treatment had been responsible.

**Reticulohistiocytoma (Type Caro/Senear).**—DENIS SHARVILL, M.R.C.P.

J. N., male, aged 50.

*History.*—Until the onset of the present illness the patient had enjoyed excellent health, suffering no major illness during thirty-five years of military service; on discharge from the Army in June 1957 he was regarded as normal at his medical examination. In April 1957 he had noticed "slight pain and fibrositis" in his right elbow, and during the summer transient severe pain in his instep. During July and August he experienced intense itching of the back for a few weeks. In September there appeared pain and stiffness in the right shoulder. The skin remained normal until November 1957, when symptomless nodules appeared in the skin of his ears and hands, increasing in numbers until early January 1958, since when they seem to be decreasing. In early January 1958 a swelling appeared on the back of each hand causing some interference with finger movements. His general health has remained good throughout, so that he has made light of his symptoms.

*On examination.*—A profuse eruption was present on the fingers, hands and wrists, and on the outer surfaces of the ears, consisting of the following elements: (1) Discrete hemispherical or flatter papules of match-head size or larger. These were of skin colour or bright red and covered by intact, but stretched and shiny, epidermis. Their consistency was firm to very hard. They were attached to the epidermis but not deeply, although the lack of subcutaneous fat on the helices made them seem fixed in those sites. (2) Rather larger streaks, macules, and plaques of larger size—up to 1 cm. or more—of a dusky red or reddish purple hue. (3) Striking lesions of the finger nail-folds just proximal to the nails, 2 to 3 mm. in width and stretching like bands across the digits; these were brownish red in colour and very firm. All the above lesions were painless and non-tender. On the dorsum of each hand was a poorly defined, broad-bean-sized swelling, attached to the extensor tendons; these were slightly tender, and there was limited flexion of the fingers, especially on the left. The right shoulder joint was completely fixed, scapular movement only being present. There was no clinical evidence of involvement of other joints. General examination showed no other clinical abnormalities; there was no evidence of thyroid disorder.

*Investigations.*—The following investigations and tests gave normal or negative results: X-rays of right shoulder region and chest. Hæmoglobin, E.S.R., total and differential white cell count. Serum cholesterol and calcium. Serum proteins, by chemical and electrophoretic investigation. Liver function tests. Rose-Waaler test.

Serum uric acid: 8·6 mg./100 ml. Serum anti-streptolysin "O" titre: 180 units/100 ml.

*Histology* (Dr. V. H. Bowers).—Reticulohistiocytoma. In the centre of the lesion the dermis is packed with multinucleate giant cells, separated from one another by only a few fine collagen fibres, and the overlying epidermis is thinned and has lost its rete ridges. In the dermis at the periphery of the lesion the giant cells are separated by broad strands of collagen, and in a few sections a single small aggregation of lymphocytes is seen in this region also. No other inflammatory cells are present. The giant cells are rounded or oval, but their shapes are modified by the pressure of adjacent cells and fibres. They range in size from 15 microns in diameter to 65 by 40 microns. The smallest cells contain a single nucleus, and the largest about 15 nuclei in each, quite irregularly arranged, and generally the larger the cell the more numerous the nuclei. The cell cytoplasm is mauve in colour in the H. and E. sections, apparently taking both stains; it is almost homogeneous, but with a barely visible fine reticular or vacuolated appearance in a few cells, and a faint basophilic smudging in others. The nuclei are round, oval or slightly indented, and they range in size from 5 microns in diameter to 13 by 10 microns. Many show a well-defined nuclear membrane, with a stippled chromatin pattern. Almost all have a single large, rounded nucleolus about 2 microns in diameter. No Nissl material or nerve axons were demonstrated. The whole of this biopsy was blocked in paraffin, and no tissue was available for frozen sections to stain for sudanophil material.

*Cytodiagnosis.*—Multinucleate giant cells were readily demonstrated in stained smears of scrapings from a nodule. These cells contained no sudanophil material.

*Postscript* (5.3.58).—During the month following presentation the patient received large doses of vitamin A, 480,000 units daily. At the end of this time the nodules had disappeared completely from the hands and fingers and largely from the ears. The tendon sheath swellings had also subsided. The condition of the joints, however, had worsened alarmingly, the other shoulder, both elbows, both wrists, most fingers, and both knees being involved. The pain and stiffness were such that the patient was unable to rise from a chair or to walk more than a few steps. Clinical examination of these joints showed a full range of passive movement with slight crepitus and a remarkable lead-pipe rigidity suggesting muscle spasm. X-rays were still normal. After forcible manipulation of the right shoulder under general anæsthesia a full range of painless movement was obtained, and has so far lasted for ten days. An injection of hydrocortisone into a knee-joint also gave full painless movement. Further special investigations and treatment are at present being carried out in hospital.

ADDENDUM (20.5.58).—The skin is now normal except for three nodules near the right elbow. The joints are painless, movement only slightly limited, and function generally good.

In view of persistent mild dysphagia the patient was referred to Mr. J. B. Blacklay for laryngoscopic examination. He found circumscribed nodules under the mucous membrane of the epiglottis; the appearance of these was unfamiliar to him, but he considered that they might well have been of the same nature as the skin lesions.

Synovial membrane from a knee-joint was heavily infiltrated with multinucleate giant cells similar to those in the skin; no sudanophil material was seen in frozen sections.

**Dr. Robert Warin:** Dr. C. D. Evans, Dr. M. Hewitt and I have recently recorded 4 cases of this condition (*Brit. med. J.*, 1957, i, 1387), making a total of 16 recorded in the literature. Two of these cases were under the care of Dr. J. T. Ingram; one in association with Dr. E. Ritter. The eruption and histology in Dr. Sharvill's case is typical of this condition. In only one of the reported cases did the rash antedate the joint disability but after a period of two years widespread arthritis developed with areas of apparent bone destruction. It seems likely that the patient seen to-day will develop the same state. We felt the condition was related to lipoid disorders in view of the presence of striking multiple xanthelasma palpebrarum in 2 cases and that histochemical investigations indicated that the material in the large giant cells was a lipoid, probably in combination with a polypeptide. We consider the condition to be an abnormality in connective tissue cell metabolism, and not a true reticulosis.

**Dr. Sharvill:** Of the cases reported in the literature, a curiously large number have died from malignant neoplasms.

**Cutaneous Hæmangiomata and Bony Deformities (Klippel-Trenaunay and Parkes Weber Syndrome).**—J. EVERALL, M.R.C.P., and M. FEIWEL, M.R.C.P. (for G. B. MITCHELL-HEGGS, O.B.E., F.R.C.P.).

Mrs. M. P., aged 32.

*History.*—Hæmangiomata of the umbilicus first noticed at the age of 6, followed by similar lesions on the right leg from the age of 11 and later about the face and mucous membranes of the mouth. Hæmangiomata of the legs treated with radiotherapy at Sheffield in 1942 and

similar lesions about the mouth and nose removed surgically at Sheffield in 1949. Severe epistaxis during childhood. No history of epilepsy. Menses regular. Married nine years, no children. General health satisfactory.

*Family history.*—Parents not related. One half-sister had epistaxis in childhood.

*Previous illness.*—Pneumonia, varicella, pleurisy.

*On examination.*—Discrete, bluish, small cavernous hæmangiomata about the muzzle area of the face, tongue and mucous membrane of the mouth. Similar lesions about the umbilicus and on the tips of the first and fifth right toes. Some superficial varicosities about the back of right calf. Multiple radiotherapeutic scars on right thigh and leg. Right leg longer and warmer than left. Right leg showed bony enlargement of the tissues along the right anterior tibial surface, associated with some enlargement of the tissues of the right ankle and right lower leg compared with the left. Multiple superficial venules about the right ankle and across the shoulders. Loud systolic murmur in the precordial region, loudest at apex. No cranial bruits heard. Blood pressure 170/75. Urine normal.

*Investigations.*—E.S.R. 6 mm. in the first hour (Westergren). Blood count normal. X-ray of right lower leg shows small phlebolith-like opacities in the subdermal tissues of the limb at several sites. Right tibia substantially longer than the left and shows periosteal new bone formation of long standing at two distinct sites.

X-*rays.*—Chest: There are irregularities in the right fourth, fifth and eighth ribs anteriorly. These changes are a mixture of expansion, very localized rarefactive foci and marginal sclerotic changes with new bone formation.

Lateral film of right tibia: Shows considerable anteromedial periosteal new bone formation and in the immediately adjacent soft tissues groups of phlebolith-like structures are seen.

Skull shows peculiar appearances of the dorsum sellæ and the posterior clinoids. Hands normal.

ECG and EEG normal.

**Dr. Feiwel:** When this patient was shown at St. John's Hospital I asked how the angioma at the corner of the mouth should be treated, whether by X-rays or by surgery? Those on the legs have responded to X-ray therapy but have left demarcated areas of atrophy. Professor C. G. Rob, who has seen her, suggested surgery but I felt there might be difficulties.

**Dr. R. T. Brain:** I suggest that about 3 minims of tincture of iodine should be injected into the middle of the lesion. I have treated similar lesions very satisfactorily.

The following cases were also shown:

**Metastasizing Sweat-gland Sarcoma.**—Dr. G. Allen, Mr. Norman Tanner, and Dr. M. Feiwel.

**Scirrhous Sweat-gland Adenocarcinoma of Lip.**—Dr. M. Feiwel and Dr. H. Haber.

**Jessner's Lymphocytic Infiltration of the Skin, associated with Chronic Urticaria.**—Dr. Robert Warin.

**Purpura Associated with Hyperglobulinæmia and Systemic Lupus Erythematosus.**—Dr. S. Reiss and Dr. M. Feiwel.

**Sarcoidosis.**—Dr. R. H. Marten (for Dr. D. I. Williams).

**Tuberculosis Cutis Colliquativa Ulcerosa.**—Dr. R. S. Francis and Dr. M. Feiwel.

**(1) Onchocerciasis. (2) Subcorneal Pustular Dermatosis.**—Dr. I. Sarkany.

**Parapsoriasis Lichenoides.**—Dr. P. J. Hare.

**Porokeratosis (Mibelli).**—Dr. R. H. Marten (for Dr. Sydney Thomson).

**Angiomatous Nævus of the Gums.**—Dr. D. I. Williams.

**Erythema Annulare Figuratum.**—Dr. J. Everall (for Dr. G. B. Mitchell-Heggs).

# Section of Proctology

President—HENRY R. THOMPSON, M.A., M.B., F.R.C.S.

[*February* 12, 1958]

## Ano-rectal Anatomy

By Professor E. W. WALLS, M.D.

*London*

BEFORE proceeding to report briefly on certain observations made on the pelvic splanchnic nerves and on the epithelial lining of the anal canal, I will indicate, in response to a request, what anatomists understand these days by the rectum. Anyone conversant with the vagaries of anatomical terminology will appreciate the feeling which prompted the plea; nor is it so simple as it might seem, for apart from changes in the names themselves there has been considerable inconsistency in their use.

According to current terminology the descending colon extends from the spleen to the left side of the brim of the true pelvis, and from there the pelvic colon continues as a somewhat variable loop suspended by the pelvic mesocolon to the middle of the third piece of the sacrum—the point at which the rectum is now considered to begin. In former days, however, the rectum was regarded as commencing at the left sacro-iliac joint, and the peritoneal fold which attached it between this level and the middle of the sacrum was called the meso-rectum; the name sigmoid colon was given to that part of the gut between the left iliac crest and the true pelvic brim. Thus defined, the sigmoid consisted of a proximal part lying in the left iliac fossa covered by peritoneum on its front and sides, and a distal portion of greatly variable length forming a loop, the sigmoid loop or flexure, provided with a mesocolon. This mesocolon together with the meso-rectum are now referred to as one unit, the pelvic mesocolon.

In justification of the present view it may be instanced that the pelvic mesocolon ceases at the third piece of the sacrum, that the appendices epiploicæ and the sacculations characteristic of the colon disappear at this level, and finally that the superior rectal (hæmorrhoidal) artery divides into two branches at the same point.

It is of interest and importance to recall that in 1830, when Houston first gave an account of the valves which bear his name, he described one of the valves as lying on the right "at the upper end of the rectum"; to-day, of course, it would be described as lying within the pelvic colon. This in itself would not matter greatly except that, as Silver (1955) has pointed out, when Houston's words are reproduced in modern accounts of the region "the reader cannot be sure whether they should be interpreted in the sense in which Houston used them, or in the light of the revised terminology".

### THE PELVIC SPLANCHNIC NERVES

These nerves, also called the nervi erigentes, spring from the anterior primary rami of the sacral nerves, their origin usually being given as the II and III, or III and IV. Although their course is well known, Dr. J. Caria Mendes, at present in this country on study leave from Portugal, has carried out a number of dissections in my Department with the special object of investigating how practicable it would be to remove the rectum without damaging the parasympathetic innervation to the urogenital system. In the formalized cadavers on which he worked it was a matter of no great difficulty to trace the nerves from their origin to where they join the corresponding pelvic (sympathetic) plexus on the side of the rectum. In fourteen specimens he found the nerves arose from the III and IV sacral nerves, in no case from the II, and he also noted that running with them in a number of specimens there were considerable contributions from the sacral portion of the ganglionated sympathetic trunk. So closely did the plexus hug the rectum that he was forced to the conclusion, with which I concur, that removal of a rectum affected by carcinoma without serious damage to the parasympathetic pelvic innervation would be a matter of immense difficulty if not impossibility.

### THE EPITHELIAL LINING OF THE ANAL CANAL

The zone to which I wish to direct attention is that above the level of the anal valves, for it was here that I found the greatest variability in epithelial type to occur. On average

the zone in the adult measures 17 mm., and in all of 20 specimens examined the upper part was lined for a variable extent (4–16 mm.) by rectal-type mucosa. The epithelium between the level at which intestinal mucosa ended and the line of the valves, a region which varied from 1–9 mm. in extent, was, however, not of constant type. In some cases stratified columnar epithelium was met with, while in others the epithelium was stratified squamous. This is not the whole story, for in some specimens several different types of epithelium succeeded one another. Thus, stratified squamous of 12 layers or more might be seen to merge into stratified columnar, or into a low stratified polygonal of only 3 or 4 layers. On occasion patches of simple columnar were also encountered in this zone, while in places the appearance of transitional epithelium was suggested.

The wide range of epithelial types which may be found in this zone of the anal canal must be a matter of some importance to pathologists called upon to report on sections from this region, and it is hoped that the findings stated briefly here may prove of service in this connexion.

REFERENCES

HOUSTON, J. (1830) *Dublin Hosp. Rep.*, **5**, 158.
SILVER, P. H. S. (1955) *J. Anat., Lond.*, **89**, 217.

## The Peutz-Jeghers Syndrome

By THOMAS L. DORMANDY, M.B., B.Sc., F.R.C.S.Ed.
*Captain, Royal Army Medical Corps*

DR. JOHANNES PEUTZ was 71 when he died a few days before Christmas, 1957. He was born in Gröningen and studied medicine at Utrecht. After postgraduate work at a number of Continental universities he settled in practice in The Hague where he became a founder of St. John's Hospital. For many years he was Chief Physician to that hospital. Many honours, including the Fellowship of the Dutch Royal Society, bear witness to the high regard and affection in which he was held in his own country. Internationally his name is now linked with the syndrome of gastro-intestinal polyposis and muco-cutaneous pigmentation which he was the first to describe (Peutz, 1921). The genealogical table of his patient covers three generations with 7 proven and 3 probable cases of the syndrome. 3 members of the family also had nasal or bladder polyps—hence Peutz's original title of "visceral" polyposis.

Like many rare diseases, Peutz's syndrome needed several rediscoveries before it became widely recognized. Greatest credit for this, as well as for establishing the syndrome as a definite clinical entity, must go to Jeghers, McKusick and Katz (1949). They not only gave a masterly account of 10 personal cases; but they also uncovered from the medical, surgical and dermatological literature of the past, several other "probables" and "possibles", including 2 cases reported by Sir Jonathan Hutchinson in 1896. The first patient to be diagnosed in this country—though not the first to be described—was presented to the Clinical Section of this Society by Mr. Norman Tanner in 1951. It is now clear that the abnormal gene responsible for the syndrome is of world-wide distribution: some of the earliest case-reports came from India, South Africa, and the Middle East.

The Peutz-Jeghers syndrome has three cardinal features—gastro-intestinal polyposis, a characteristic pattern of melanin pigmentation of the skin and mucous membranes, and familial transmission by a Mendelian dominant gene (or genes). Gastro-intestinal polyposis does not invariably involve all parts of the gastro-intestinal tract: but it *may* affect any part and sooner or later it always affects the small intestine. According to the segments involved various regional classifications have been suggested; but they may lead to errors in diagnosis and in management. There is a silent time-interval of many years between the peak incidence of symptoms from polyps in the rectum, the small intestine, the colon, and the stomach. The polyps in these various parts seem to erupt at different ages; and some—especially the rectal polyps of childhood—may regress and disappear spontaneously after a few years (Andrén and Frieberg, 1956). In the jejunum and ileum alone the naked-eye growths do not appear synchronously: after the first crop has appeared many months or years may elapse before the next sprouts out; and at operation two polyp-bearing segments are usually separated by still normal-looking gut. This mode of spread is a strong argument against prophylactic "clearing" operations on symptomless patients.

A woman patient, who is now 57, started to have attacks of abdominal colic at the age of 20. For ten years she had numerous negative investigations; and in 1930 she entered a mental home as a voluntary "neurotic" patient. There she was struck down by a particularly violent attack, which led to her first laparotomy. Two small-intestinal intussusceptions were found and resected; and more polyps were identified by palpation in her small intestine and colon. Six months later she was free from symptoms; but, anxious to forestall future episodes before resuming her career as a school-

teacher, she was easily persuaded to "get rid of all her polyps." Accordingly, two elective operations were performed: her small intestine was "cleared" through a number of enterotomies at the first; and her right hemi-colon was removed at the second. After three years of good health she was seized by another attack; and the same surgeon who had operated on her before found at laparotomy another ileal intussusception studded with polyps. This was resected. During the past twenty-two years she has been symptom-free; and, until fourteen months ago, yearly barium investigations have shown no abnormality. Her two most recent double-contrast barium enema pictures, however, again show several moderate-sized polyps in what is now her terminal ileum.

Fortunately, "clearing" operations are not only unlikely to be successful in preventing future obstructive episodes; they are also unnecessary from the point of view of malignant change. In sharp contrast to polyps of the colon and, perhaps, the stomach, small-intestinal polyps do not become cancers—not, at least, in the clinically accepted sense. Histologically many show the classical features of an early, well-differentiated adenocarcinoma, especially apparent invasion of the submucosa and muscularis; but the clinical follow-up always casts doubt on the pathological diagnosis (Dormandy, 1958). One can only guess at possible explanations for this striking dissimilarity between the natural history of polyps in the small and large gut (even in the same patient): here I would merely like to dismiss two obvious ones. First, patients with small-intestinal polyps do, as a rule, live into the cancer age: indeed, many die from cancer arising from one of their rectal or colonic polyps. Second, I do not think that they are saved from developing small-intestinal carcinomas by intussusceptions which precipitate, as it were, timely operations. It is true that the rare and rapidly fatal primary small-bowel carcinoma rarely causes intussusception; but most patients with adenomatous polyps—whether these are frankly innocent or apparently malignant—suffer from self-reducing intussusceptions for many years before they are diagnosed. "There is", as the *Lancet* commented, "something very curious about the resistance of the human small bowel to malignancy. Its mucosa is extensive and it has a high mitotic rate. It lies in direct continuity with the mucosæ of the pylorus, bile-ducts, pancreatic ducts, and colon—areas of high cancer-incidence. If carcinogenic hydrocarbons are fed to rats, those few alimentary adenocarcinomas which do arise are largely confined to the small intestine. [Yet] . . . there is no more remarkable example of this apparent cancer resistance than the uniformly good prognosis of these polypoid lesions, which at any other site of the body could be so confidently labelled pre-malignant [and which are, in fact, often labelled malignant by the pathologist]" (*Lancet*, 1957).

I think that the origin of many small-intestinal polyps from the deeper layers of the bowel-wall accounts for most histological diagnoses of malignancy. Examining serial sections of two operation and post-mortem specimens of small bowel, I found a number of areas of microscopic intramural adenomatosis in parts of the gut which looked normal or almost normal to the naked eye. These microscopic adenomas vary in complexity from simple "vesicles" to more substantial nodules: they tend to be grouped together (often around one or two naked-eye polyps): they interrupt the continuity of the muscle coat: and many show some degree of cellular irregularity (or immaturity) and great mitotic activity. The apparent "invasion" of the deeper layers of the bowel-wall by large naked-eye polyps would seem to reflect their origin rather than an ominous late development in their natural history.

Intussusceptions, often compound, sometimes multiple, occasionally retrograde, almost invariably transient, are the characteristic complication of small-intestinal polyposis: indeed, life with small-intestinal polyps, or even a solitary polyp, could be described as a succession of acute, subacute and chronic intussusceptions. They are the pathological basis of a highly characteristic clinical picture. The patients frequently give a history, going back with intermissions over many years, of brief but sometimes extremely severe attacks of green-apple type of colic. These attacks can strike at any time; but often they come on with great regularity a few minutes after meals, or, even more commonly, shortly after getting out of bed in the morning. Many patients say that during the attacks they have a sensation of a lump or lumps rolling about in their abdomen: and some maintain (probably rightly) that they can even palpate a mass moving about. As a rule the attacks subside spontaneously; or they can be cut short by the patient performing some physical contortion, such as doubling over a chair, or even by pressing on various parts of the abdomen. It can be quite frightening to see a mother vigorously massaging the abdomen of her ill child: but there is no doubt that this can be effective. (In 1925 Barrington-Ward concluded a case report of multiple small-intestinal tumours with the remark, "I have not seen a case before in which it was possible to reduce intussusceptions by simple manipulation through the abdominal wall: [yet] this was done on at least three occasions by two different observers".) The attacks of pain are often heralded by flourishes of loud borborygmi: and during periods of intermission explosive rumblings can be not only a source of social embarrassment but also a warning of more attacks to come.

The transience of the intussusceptions accounts for the disconcertingly rapid changes

in the physical findings. A lump felt with the utmost certainty may not be demonstrable an hour later: an easily palpable or even visible mass, described by the family doctor or the casualty officer as "fixed" in the right iliac fossa, may have moved to the left hypochondrium by the time the patient is examined in the ward. Aspersions may be cast on the clinical acumen of earlier observers, when, in fact, the very impermanence of the physical signs should provide a clue to the diagnosis.

A curious feature of these small-intestinal intussusceptions, which cannot be explained by the mechanisms postulated by Wardill (1925) or Raiford (1932), is that some contain no polyps, even though many polyps may be present in other segments of the bowel (Dubourg *et al.*, 1952). The explanation, I think, lies in the microscopic derangement of the gut-wall, which is far more extensive than the naked-eye picture would suggest: areas of micro-adenomatosis could certainly interfere with normal peristalsis and initiate abnormal waves of contraction.

Melanin pigmentation is the second cardinal feature of the Peutz-Jeghers syndrome. Its cutaneous component is the more striking but the less constant: it consists of light-brown to black macules, varying in number from one or two to many hundred, and in size from those just visible to others three or four millimetres in diameter. Their margins are clearly outlined: and they are characteristically grouped around the mouth, the nostrils and the eyes. The fingers, the palms, the toes and the soles of the feet occasionally carry a few. The mucosal pigmentation is often less conspicuous and lighter in shade; but, as Jeghers insisted (Jeghers *et al.*, 1949), it is the *sine qua non* of the syndrome. The lips and cheeks are always involved; and dark patches can sometimes be found on the palate, the fauces and the conjunctivæ. The polyps and the intestinal mucosa are not pigmented. Wherever they are, the macules are level with the skin or mucous membrane, they are non-hairy, non-vascular and non-irritating: and their number and distribution bear no relationship to the number of polyps or to the severity of the gastro-intestinal symptoms. It is surprising how often extensive facial and especially buccal pigmentation passes unnoticed by doctor, dentist and even close relatives: and what should be a spot diagnosis in more senses than one is not usually made until after laparotomy. On the other hand, the cutaneous spots can be a real nuisance: one child's life was made a misery at school because of his continuously "dirty" lips; and at least one patient has undergone a plastic operation on her lips to improve appearances (Edwards, 1958).

The cutaneous pigmentation is usually present at birth and begins to fade around puberty: but cases where both the macules and the digestive symptoms did not appear until old age are on record (Troxell, 1954). Contrary to what has been suggested by earlier observers, the pigmentation and the syndrome are not confined to dark-complexioned people: amongst 21 cases investigated by myself 4 were fair-haired (Dormandy, 1957).

Like polyposis coli, the Peutz-Jeghers syndrome is occasionally associated with other congenital and sometimes hereditary abnormalities. Apart from bladder and nasal polyps mentioned by Peutz and more recently by Hafter (1954), I have encountered examples (amongst my own patients or in the literature) of associated bronchial adenomatosis, a variety of skeletal and cutaneous defects (especially mild finger clubbing), congenital heart disease, extensive small-intestinal diverticulosis, retarded development, and ovarian disease (Dormandy, 1958; Staley and Schwarz, 1957). Also, like polyposis coli, many cases appear sporadically: and in some members of affected families the pigmentation or the polyposis alone may manifest itself. The exact pattern of the genetic transmission remains to be elucidated.

## REFERENCES


ANDRÉN, L., and FRIEBERG, S. (1956) *Acta radiol., Stockh.*, **46**, 507.
BARRINGTON-WARD, L. E. (1925) *Brit. J. Surg.*, **12**, 48.
DORMANDY, T. L. (1957) *New Engl. J. Med.*, **256**, 1093, 1141, 1186.
—— (1958) In: Modern Trends in Gastroenterology (2nd ser.). Edited by F. Avery Jones. London.
DUBOURG, G., DUBARRY, J., CARLES, J., GAILLARD, P., and DELBES, P. (1952) *Arch. Mal. Appar. dig.*, **41**, 540.
EDWARDS, J. H. (1958) Personal Communication.
HAFTER, E. (1954) *Gastroenterologia*, **84**, 341.
HUTCHINSON, J. (1896) *Arch. Surg., Lond.*, **7**, 290.
JEGHERS, H., MCKUSICK, V. A., and KATZ, K. H. (1949) *New Engl. J. Med.*, **241**, 933.
*Lancet* (1957) ii, 475.
PEUTZ, J. C. A. (1921) *Ned. Maandschr. Verlosk. (Geneesk.)*, **10**, 134.
RAIFORD, T. S. (1932) *Arch. Surg., Chicago*, **25**, 122.
STALEY, C. J., and SCHWARZ, H., II (1957) *Surg. Gynec. Obstet.* (Internat. Abstr.), **105**, 1.
TANNER, N. C. (1951) *Proc. R. Soc. Med.*, **44**, 450.
TROXELL, M. A. (1954) *Arch. Derm. Syph., Chicago*, **70**, 488.
WARDILL, W. E. M. (1925) *Brit. J. Surg.*, **13**, 158.

# Treatment of Ulcerative Colitis with Local Hydrocortisone

By S. C. TRUELOVE, M.D., M.R.C.P.
*Oxford*

A CONTROLLED therapeutic trial of patients with ulcerative colitis carried out by the co-operation of a number of physicians showed that cortisone *by mouth* increased the chances of a patient going into clinical remission within six weeks of starting medical treatment. (Truelove and Witts, 1954, 1955).

The finding that cortisone by mouth is beneficial in cutting short an attack of ulcerative colitis immediately suggested the possibility of using hydrocortisone locally in the colon. It was first necessary to find the best way to introduce hydrocortisone into the colon without it immediately being thrown out by the inflamed organ. I decided to use a drip into the rectum, making use of a blood transfusion giving-set slightly modified to carry a rubber catheter at the end for actual insertion into the rectum. Subsequent experience has shown that this is effective in all but a very few patients. Patients who are not severely ill can carry out this treatment at home without difficulty.

Since 1955 I have given 107 courses of treatment with local hydrocortisone to 80 separate patients, a number of the patients having been treated more than once. These treatments can be divided into four main groups (Table I). The first three groups represent formal

TABLE I.—TREATMENT OF U.C. WITH LOCAL HYDROCORTISONE UP TO JANUARY, 1958

| | Treatment | No. of courses of treatment | Rapid remissions | |
|---|---|---|---|---|
| I | Hydrocortisone (free alcohol) in dilute alcoholic solution. 60–120 mg. HC nightly | 21 | 14 | Truelove (1956) |
| II | Hydrocortisone hemisuccinate sodium in saline. 100 mg. HC nightly | 18 | 11 | Truelove (1957) |
| III | Controlled trial of HC-HSS for 1 week followed by known HC-HSS + antibiotics for 2 weeks | 40 | 29 | To be published |
| IV | Miscellaneous treatments not included in I–III | 28 | | Severe cases<br>U.C. in pregnancy<br>Juvenile cases<br>Long-continued treatment |

studies, the first two of which have been reported (Truelove, 1956, 1957) while the third will be reported in detail shortly (Truelove, 1958). The fourth group consists of a miscellaneous collection of patients.

The first study (Row I in Table I) involved 21 courses of treatment using hydrocortisone itself. Because hydrocortisone has a low solubility in water (though much greater than that of cortisone) the manufacturers supplied it dissolved in 50% ethyl alcohol, in which it is quite soluble. This was diluted with ten times its volume of saline for actual use in the colon and was dripped into the rectum from the modified blood transfusion set (Fig. 1). The result of

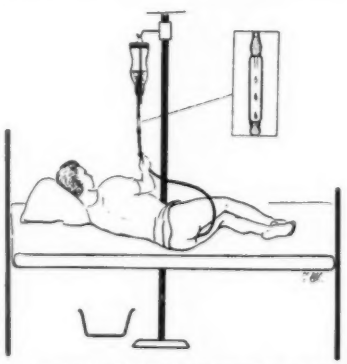


FIG. 1.—Method of self-administration of rectal drip.

this form of treatment was apparently good, because in 14 instances there was rapid clinica remission, i.e. within a few days.

The number of patients who responded to the treatment in this first study seemed to me quite encouraging. The sigmoidoscopic appearances also improved in parallel with the clinical responses. However, there was an odd discrepancy in that the histological responses, as judged by small biopsy specimens taken from the lower colon by means of an instrument devised for this purpose, did not show a corresponding improvement. This raised the possibility that the alcohol which formed part of the diluent for the hydrocortisone might itself be having a bad effect upon the inflamed colonic mucosa and preventing it from healing.

Fortunately, at about this time, Glaxo Laboratories were able to give me hydrocortisone hemisuccinate sodium, which is highly soluble in water. From Row II of Table I, it will be seen that the second study involved 18 courses of treatment given with this agent. The clinical response to hemisuccinate was closely similar to that obtained with hydrocortisone itself for there were 11 rapid remissions. The sigmoidoscopic appearances improved in parallel with the clinical response. Moreover, a favourable clinical response was accompanied by a definite improvement in the colonic mucosa, as judged from biopsy specimens. It therefore appears that a water-soluble compound such as the hemisuccinate is better than hydrocortisone itself, because, on first principles, it seems wise to choose an agent with which the actual diseased tissue shows evidence of reverting toward normality.

At this stage it seemed imperative to put this form of treatment to a formal test to make quite sure that the favourable judgment which I had formed on clinical impressions alone was indeed true. I therefore carried out last year a planned therapeutic trial involving 40 courses of treatment. The first part of the trial involved the use of either real hydrocortisone hemisuccinate or a similar-looking inert preparation. These were prepared by the manufacturers and nobody at Oxford knew which was which until the study was finished. The patients were allotted at random to one or other and this "blind" part of the trial lasted for one week. In every case, this was followed by two weeks of treatment with known hydrocortisone hemisuccinate sodium, together with penicillin and streptomycin added to the rectal drip, because I also wished to find out whether the addition of antibiotics would improve the action of the hydrocortisone and bring into remission cases that did not respond to hydrocortisone alone. At the end of the first week, out of 20 courses of treatment given with the inert preparation, only one resulted in clinical remission; whereas out of 20 courses of treatment with real hydrocortisone hemisuccinate, 11 patients were in remission. The difference is considerable and is statistically highly significant ($P < \cdot 01$). A fortnight later, after known treatment with hydrocortisone and antibiotics, the two groups were closely similar. We may therefore take it as reasonably certain that hydrocortisone hemisuccinate dripped into the rectum has a real effect in bringing about clinical remission in quite a large proportion of the patients. In other words, its action is pharmacological and not due to any placebo or psychological effect.

Antibiotics do not make much overall difference, sometimes being helpful and sometimes being deleterious, but this point will not be discussed further here except to say that they should not be used routinely.

Group IV of the treatments shown in Table I is a miscellaneous collection of patients who have not been included in any of the previous three studies for a variety of reasons. Only one or two points will be mentioned:

*Severe cases.*—In general, the local treatment has been used for patients suffering only from mild or moderate attacks of ulcerative colitis. This has been done for two reasons:

(1) A severe attack of ulcerative colitis is a dangerous illness and it seems right to gain a good deal of experience with any new form of treatment in the less severe cases before applying it to those patients who are gravely ill.

(2) An additional reason has been that a second large-scale trial is taking place in 12 hospital centres in this country of the systemic use of cortisone and of ACTH and the more severe cases that I have seen have been admitted to this national trial.

However, a few patients with severe attacks have been given the local treatment, particularly when they have failed to respond to the corticoids used systemically. In general the results have been highly favourable. However, various technical problems arise when treating severe cases by this method: these are being studied at present.

### Ulcerative Colitis in Pregnancy

It is known that ulcerative colitis in pregnancy can be severe and is at the least a grea inconvenience and trouble to the patient if the symptoms persist throughout the pregnancy Two patients having symptoms during pregnancy have been treated with a nightly rectal dri of hydrocortisone which has been continued until after the baby has been born. The result have been excellent in both patients.

### Juvenile Cases

I do not see many children with this disease but three that I have seen in the last year and have treated by this method have all done well. These have been treated in the same way as the pregnant patients, in that treatment has been continued for months rather than for two or three weeks. I mention this point because I think it possible that this will be the future method of choice when a favourable response is obtained to local treatment.

### Long-term Results

The use of hydrocortisone locally, even when it brings about remission, does not mean that these patients are going to be free from further attacks of the disease. Indeed, there is no known medical treatment which will guarantee freedom from recurrent attacks once a person has suffered from this illness. However, it should not be thought that rapid relapse is particularly likely to occur when the treatment is stopped. Indeed, immediate relapse is unusual although relapse over the course of the next few months is fairly frequent. Some patients have remained in perfect remission after a single course. For example, the first patient who was treated two and a half years ago has been symptom-free ever since.

Some idea of the early long-term results can be gained from considering what has happened to 15 patients who responded well to treatment in 1955 and 1956. 6 of them have remained in perfect remission; 7 have had one or more recurrences but have responded swiftly to further courses of local treatment; and 2 have had recurrences which did not respond to a further course so that alternative treatment was necessary.

### REFERENCES


Truelove, S. C. (1956) *Brit. med. J.*, ii, 1267.
—— (1957) *Brit. med. J.*, i, 1437.
—— (1958) In preparation.
——, and Witts, L. J. (1954) *Brit. med. J.*, ii, 375.
——, —— (1955) *Brit. med. J.*, ii, 1041.


## Observations on the Management of Idiopathic Proctitis [*Abridged*]


By A. C. Newell, M.D., M.R.A.C.P., and F. Avery Jones, M.D., F.R.C.P.
*London*


These observations are part of a larger study of the natural history of idiopathic proctitis, and are based on the study of 150 patients attending the out-patients at St. Mark's Hospital in the six and a half year period from January 1951 to June 1957. They were patients with typical sigmoidoscopic appearance but with minimal X-ray evidence of disease of the colon itself although undoubtedly a proportion of patients had the same inflammatory process extending upwards into the sigmoid. In the series of 150 there were 94 females and 56 males. Of the 150 cases follow-up information had been obtained from all but 6 of them; 50 at the time of last examination had continuing symptoms and of these 12 had had extension of the disease process often involving the entire bowel and necessitating surgical treatment.

The view was firmly established from this survey that idiopathic proctitis was one and the same disease as ulcerative colitis but in a localized and milder form.

Observations were made on the effect of treatment with prednisone and, initially, a comparison was made between three weeks' treatment with calcium lactate and the same period with prednisone taking alternate cases. Of the 13 patients treated with calcium lactate 9 were not improved or worse at the end of three weeks compared with only 1 out of 10 treated with prednisone who had not improved or got worse. Altogether 44 patients were treated with prednisone and at the end of treatment 16 had no symptoms with normal sigmoidoscopic appearance, 12 had no symptoms with low-grade proctitis present, 11 had persistent symptoms and signs but improvement in both, only 5 showed no improvement. Within three months, however, another 11 had relapsed and needed further treatment. The patients were all treated in the out-patients' department starting with 20 mg. three times a day for one week reducing the dose to 15 mg. three times a day for the second week and then 10 mg. three times a day for another two or three weeks subsequently tailing the dose off. There were side-effects in half the patients but these proved temporary only. One patient developed diabetes, 5 had indigestion and 6 a moderate degree of acne. Symptoms all responded to dose reduction and cessation of treatment.

## BOOKS RECEIVED FOR REVIEW

**Bensley (E. H.),** and **Joron (G. E.).** Handbook of treatment of acute poisoning. 2nd edit. pp. xii+212. Edinburgh and London: Livingstone. 15s. 0d. 1958.

**Boursnell (J. C.).** Safety techniques for radioactive tracers. pp. xii+68. Cambridge: University Press. 7s. 6d. 1958.

**Cohen of Birkenhead (Lord).** Sherrington: physiologist, philosopher and poet. (The Sherrington Lectures: IV.) pp. xiv+108. Liverpool: University Press. 17s. 6d. 1958.

**Davison (W. C.),** and **Levinthal (J. Davison).** The compleat pediatrician. pp. vi+257. London: Staples. 35s. 0d. 1958.

**Haynes (B. G.).** Autonomic dyspraxia. pp. viii+122. London: Lewis. 15s. 0d. 1958.

**Heymans (C.),** and **Neil (E.).** Reflexogenic areas of the cardiovascular system. pp. viii+271. London: Churchill. 56s. 0d. 1958.

**Hoff (F.)** Behandlung innerer Krankheiten. 8th edit. pp. xii+733. Stuttgart: Thieme. DM. 59.50. 1958.

**Martindale (W.).** The extra pharmacopœia. Vol. 1. 24th edit. pp. xxx+1695. London: Pharmaceutical Press. 65s. 0d. 1958.

**Naundorf (G.).** Versuch der Darstellung des Entwicklungsgeschehens. pp. 36. Hamburg: Naundorf. 1958.

**Penfield (W.).** The excitable cortex in conscious man. (The Sherrington Lectures: V.) pp. ix+42. Liverpool: University Press. 10s. 6d. 1958.

**Russell (W. Ritchie).** The physiology of learning. pp. 28. Edinburgh: Royal College of Physicians. 1957.

**Stuart-Harris (C. H.),** and **Hanley (T.).** Chronic bronchitis, emphysema, and cor pulmonale. pp. 252. Bristol: Wright. 42s. 0d. 1957.

**Sugar (H. S.).** The glaucomas. 2nd edit. pp. x+516. London: Cassell. £5 5s. 0d. 1958.

**Wallerstein (R. S.), *et al.*** Hospital treatment of alcoholism. pp. 212. London: Imago. 42s. 0d. 1957.

**Walsh (F. B.).** Clinical neuro-ophthalmology. 2nd edit. pp. xvi+1294. London: Baillière. £11 11s. 0d. 1957.

**Weber (F. Parkes).** Medical teleology and miscellaneous subjects. pp. viii+86. London: Lewis. 15s. 0d. 1958.

# Section of Orthopædics

President—J. A. CHOLMELEY, F.R.C.S.

[*February* 4, 1958]

## Recurrent Synovitis of the Knee

By PETER R. FRENCH, F.R.C.S.
*London*

THE purpose of this communication is to trace the progression from trivial injuries to the knee, to recurrent synovitis and the eventual development of osteoarthritis. I believe that if we explored the knee earlier we might delay the development of osteoarthritis. This paper is based on the findings in the last 305 knees operated on in St. George's Hospital, London, and St. Peter's Hospital, Chertsey.

A joint effusion occurs for two main reasons; the first is a micro-organism and the second internal derangement. It is a commonplace that repeated locking of a knee by a bucket-handle tear of a meniscus causes recurrent effusion into the joint. What is not so well realized is that the condition labelled chronic non-specific synovitis is in the majority of cases also due to mechanical upset. Earlier recognition of this fact and operative intervention may postpone the development of osteoarthritis. The two main difficulties in the past have been, (1) the conditions that lead to osteoarthritis are usually present long before there is radiological evidence of them; and, (2) there has been some hesitation about performing an adequate exploration of the knee-joint. It is questionable whether quadriceps insufficiency is ever by itself a cause of swelling of the knee, and, indeed, in poliomyelitis does not produce an effusion. Synovial biopsy in the past has been made through a minute incision, synovial hyperplasia and hyperæmia are noted, and microscopically there is a non-specific inflammatory change. The guinea-pig survives the inoculation.

The clinical picture is one of recurrent swelling of the knee, with aching pain which is aggravated by activity and settles with rest. There is often stiffness after sitting and there may be painful giving way due to a frayed meniscus or non-radiopaque loose bodies. The knee is found to be slightly warm, may have a moderate effusion and the quadriceps is somewhat wasted. There is some limitation of movement and tenderness along the joint line and at the reflection of synovial membrane from articular margins. The localization of tenderness is often misleading, as the causative lesion may be out of reach of the palpating finger. The patient is otherwise well and no other joints are affected. Radiographs are usually normal but may show a loose body or slight irregularity in the contour of the articular surfaces. The majority settle with rest but flare with activity. Physiotherapy often aggravates the condition. The subsequent course is variable; a few are found to be disease of the synovial membrane such as villo-nodular synovitis or synovial chondromatosis. A small proportion several years later will develop polyarthritis. We are discussing the remainder.

As opposed to the old-fashioned form of biopsy, adequate exploration of this type of knee discloses lesions of the meniscus, or chondromalacia of the patella producing wearing of the articular cartilage of the femoral condyle. This is accompanied by redness of the synovial membrane and free fluid containing pieces of articular cartilage or meniscus debris.

The normal wear and tear of articular cartilage with advancing age has been described in detail; increased wear of one section of articular surface may not be discovered unless the whole of the patello-femoral and femoro-tibial articulations is exposed. Radiological evidence of cartilage wear will not be present until the changes are irreparable.

Figs. 1–3 illustrate mechanical lesions with changes in the articular cartilage associated with a non-specific inflammatory reaction in the synovial membrane.

Fig. 1 shows a worn area on the articular surface of the patella with a corresponding area of wear high up on the femoral condyle. The synovial membrane was markedly inflamed and there was free fluid in the joint containing pieces of articular debris. The radiograph was normal.

Fig. 2 shows a frayed and degenerate meniscus which is licking at the femoral condyle low down; the condyle is only worn where the meniscus is in contact with it and the articular cartilage is normal elsewhere.



FIG. 1.



FIG. 2.



FIG. 3.

Fig. 3 depicts the knee of a boy aged 14 who presented with symptoms and signs indistinguishable from a tuberculous synovitis. The history included a kick on the same knee by a cow at the age of 8. The excrescence seen on the articular surface of the patella consisted of fibro-cartilage growing from a small circular defect in the cartilage. The synovial fluid contained pieces of similar fibro-cartilage as did the synovial membrane which was taken for section. Radiographs were normal. After removal of the excrescence the knee settled down completely.

The mechanism of the lesion producing the synovitis may sometimes be in doubt. Patello-femoral wear following a recurrent dislocation of the patella is obvious; but subluxation or incongruity of the patello-femoral joint is probably commoner and less obvious. Trauma to the knee-cap leading to damage of the articular cartilage on the patella or femur must be

very common in childhood and adolescence. Again, a major incident tearing a meniscus in a footballer is easy to understand; what is less commonly appreciated is the damage that may be sustained by a meniscus in everyday use.

Microscopy of the centrifuged deposit of synovial fluid often shows fragments of articular debris. The synovial membrane shows increased vascularity with a non-specific inflammatory reaction; occasionally fragments of debris may be found incorporated in it. These findings are supported by animal experiment.

Lloyd-Roberts (1953) discussed the influences of articular cartilage shed from joint surfaces in severe osteoarthritis of the hip-joint upon the symptoms of the disease and concluded that these were due to the taking up of debris by the synovial membrane. We are concerned with earlier changes occurring in the knee. We believe that the synovial membrane is affected in mechanical upsets by acting as a scavenger and removing the pieces of debris from the joint; the debris in the synovial membrane sets up areas of inflammation not unlike a foreign-body reaction. With activity showers of articular debris are cast off; with rest the synovial membrane has a chance to settle down; hence the temporary benefit of splinting. In time, continued inflammation of synovial membrane and capsule gives rise to fibrosis which produces the clinical symptoms and signs of osteoarthritis; the latter is not commonly diagnosed, however, until there is radiological evidence of it. A frayed or damaged meniscus may destroy the articular cartilage of the femoro-tibial compartment of the knee. The patello-femoral compartment may become worn by the peculiar stresses involved in the patello-femoral joint and the susceptibility of the knee-cap to trauma; particularly is this seen in recurrent dislocation or subluxation of the patella. It is felt that earlier recognition of these conditions by exploration of the knee-joint with removal of a frayed meniscus or a worn knee-cap might do much to ward off the crippling condition of osteoarthritis of the knee.

Synovitis is the warning light. If the synovitis is recurrent or persists for more than three months the knee should be explored. This involves an adequate incision to enable one to examine the patello-femoral and femoro-tibial compartments, as a small opening often fails to disclose the pathology. This has been our practice for the last three years; we have found it rewarding and have not found an increase in the number of complications or the length of stay in hospital.

REFERENCE.—Lloyd-Roberts, G. C. (1953) *J. Bone Jt. Surg.*, **35B**, 627.

## Arthrodesis of the Great Toe

By A. C. Bingold, M.B., F.R.C.S.

*London*

Should a patient suffering from hallux valgus or hallux rigidus have an arthrodesis or an arthroplasty? As can be seen from the review of the recent literature presented in Table I there is a division of opinion; some opinions are based on very small series. The purpose of this paper is to present a simple technique of arthrodesing the first metatarsophalangeal joint together with the results of a series of 32 arthrodeses comprising both hallux valgus and hallux rigidus cases and to state the indications for either arthrodesis or arthroplasty.

Table I.—Arthroplasty or Arthrodesis of the Great Toe: Review of Recent Literature

| Authors | Treatment recommended for Hallux valgus | Treatment recommended for Hallux rigidus | No. of toes treated | Type of operation reviewed |
|---|---|---|---|---|
| Thompson and McElvenny (1940) | Arthrodesis | Arthrodesis | 14 | Arthrodesis |
| Glissan (1946) .. .. .. | Arthrodesis | Arthrodesis | No. not given | Arthrodesis |
| Smith (1952) .. .. .. | Arthrodesis | Arthrodesis | 16 | Arthrodesis |
| McKeever (1952) .. .. .. | Arthrodesis | Arthrodesis | 56 | Arthrodesis |
| Bonney and Macnab (1952) .. | Arthroplasty | Arthrodesis | 518 | Arthroplasty |
| Cleveland and Winant (1950) .. | Arthroplasty | Arthroplasty | 193 | Arthroplasty |
| Jordan and Brodsky (1951) .. | Arthroplasty | Arthroplasty | 161 | Arthroplasty |
| Cymble (1956) .. .. .. | Arthroplasty | Arthroplasty | 26 | 10 arthrodeses<br>16 arthroplasties |

*Operative technique.*—Before the operation the height of heel the patient wishes to wear is ascertained. A block of corresponding height is then placed under the unshod heel. The angle formed by the first metatarsal and its phalanx is then measured and a pattern is cut from a piece of sheet rubber. Experience has shown that if the angle exceeds 25 degrees arthrodesis should not be attempted.

Through a medial incision the first metatarsophalangeal joint is opened and the invariabl osteoarthritic medial sesamoid is removed. After resection of the articular cartilage th bone ends are shaped with special convex and concave reamers. Using the pattern it i now easy to adjust the great toe at the predetermined angle. Toe and metatarsal may b held together either with a compression device or more simply and safely with an obliquel placed screw (Fig. 1). It is wise to protect the arthrodesis in all cases with a plaster slippe



FIG. 1.—Method of holding bone ends together with an obliquely placed screw.



FIG. 2.—Footprints. Left after Keller's operation. Right after arthrodesis.



FIG. 3.—Foot of patient suffering from hallux rigidus X-rayed in the pushing off phase.

applied over ample padding. Weight bearing is not permitted until the plaster slipper, stitches and any compression device are removed at the end of four weeks. Radiographs are taken and, if the arthrodesis is solid, walking is allowed, but it may be necessary to protect the arthrodesis for a further two to three weeks with a plaster slipper on which the patient can walk. Two to three months after the operation the patient can wear his shoes again.

*Method of study*.—Each patient was personally followed up by the writer. After clinical examination the patient was shown a questionnaire with 4 subjective functional grades and asked to place himself in one of the grades. Grade I, feet normal; Grade II, much improved; Grade III, little if any improvement; Grade IV, worse.

*Hallux valgus series*.—6 patients, 2 male and 4 female, were operated on, 2 of them bilaterally so that eight great toes were available for study. The average age was 53 years. The average follow-up was 11·8 months.

The anatomical result was satisfactory in all cases although in one patient the toe had been fused at a wrong angle necessitating a second operation. The best angle of fusion was 15–20 degrees of dorsiflexion of the great phalanx. There were no non-unions. Subjectively 3 were in Grade I and 5 in Grade II.

5 patients with seven arthrodesed toes had hard skin under their arthrodesed joints which indicated active use of the first digital ray in walking. But one patient with a reversed metatarsal arch, placed in Grade II, put most of her weight on her third metatarsal head. There was no sepsis and no patient had a painful interphalangeal joint.

*Hallux rigidus series*.—22 patients, 9 male and 13 female were operated on, 2 of them bilaterally, making twenty-four great toes available for study. The average age was 45 years. The average follow-up was 14·1 months.

Subjectively 10 were in Grade I, 11 in Grade II, and 3 in Grade III. 2 patients only were dissatisfied. One of these with two arthrodesed toes was a psychopath who had been offered a leucotomy. The other was bitterly disappointed that her toe should now be fixed, although this had been explained to her before the operation. Clinically both patients had well united non-tender arthrodeses with the toe fixed at a correct angle.

The angle of fusion was satisfactory in all cases. The best angle was found to be 15–2 degrees of dorsiflexion of the first phalanx if the interphalangeal joint was normal or had flexion contracture, but if the interphalangeal joint was hypermobile, the best position o the first phalanx was in line with the first metatarsal.

patients on whom a compression device had been used had painless non-unions, one in Grade I and two in Grade II. Clinically their arthrodeses were solid. Only 7 patients with eight arthrodesed great toes had hard skin under their arthrodesed joints and first phalanges. They were, therefore, making full use of the great toe in the final stages of propulsion.

Only one patient required removal of the screw. Sepsis occurred only once necessitating curettage of a small abscess of the first phalanx. Two years later the architecture of this bone was normal, the arthrodesis was solid and the patient had no pain.

No patient had a painful interphalangeal joint. Patients with contracted interphalangeal joints could only wear a heel of a particular height, but patients with a hypermobile interphalangeal joint were not so restricted, and one patient habitually wore court shoes with 3 in. heels.

## Discussion

To understand how arthroplasty and arthrodesis relieve pain in the great toe it is necessary to examine footprints.

A successful arthroplasty for hallux valgus converts a painful great toe into a functionless but painless appendage and weight is borne on the outer four metatarsal heads (Fig. 2). This result is achieved by either Mayo's or preferably Keller's operation. Arthroplasty is the method of choice for most cases of hallux valgus but it tends to aggravate metatarsalgia by throwing an extra load on already painful metatarsal heads, and is, therefore, contra-indicated in all cases of metatarsalgia.

If the metatarsophalangeal joint of the great toe is not osteoarthritic McBride's operation, which restores the shape of the toe to normal without destroying its function, is obviously preferable.

A successful arthrodesis produces a strong great toe on which weight is borne and which plays its part in the final stages of propulsion (Fig. 2). Any tendency to metatarsalgia is therefore, lessened. Arthrodesis is of special value to patients suffering from hallux rigidus because they have an abnormal gait compressing their first great toe-joint in walking (Fig. 3). After an arthroplasty for hallux rigidus this abnormal gait persists, causing compression of the newly made joint and in active patients recurrence of pain.

The above considerations have produced the following schemes for the operative treatment of hallux valgus and rigidus (Tables II and III).

Table II.—Operative Treatment of Hallux Valgus

| Type of case | Treatment |
|---|---|
| Patients up to 45 years of age without osteoarthritis. | McBride's operation |
| Patients over 45 years of age and younger patients with osteoarthritis | Arthroplasty (preferably Keller's operation) |
| Patients with severe metatarsalgia, e.g. caused by dorsal dislocation of the second toe | Arthrodesis plus excision of painful metatarsal head |

Table III.—Operative Treatment of Hallux Rigidus

| Type of case | Treatment |
|---|---|
| Active patients— including women with hypermobile interphalangeal joints. | Arthrodesis |
| Inactive patients | Arthroplasty |

Osteoarthritis of the interphalangeal joint is an absolute contra-indication to arthrodesis. So far osteoarthritis has not been observed as a complication of arthrodesis, althoughsome of the cases were operated on more than five years ago.

## REFERENCES


Conney, G., and Macnab, I. (1952) *J. Bone Jt. Surg.*, **34B,** 366.
Leveland, M., and Winant, E. M. (1950) *J. Bone Jt. Surg.*, **32A,** 163.
Rymble, B. T. (1956) *Lancet*, ii, 1134.
Lissan, D. J. (1946) *Med. J. Aust.*, ii, 585.
Ordan, H. H., and Brodsky, A. E. (1951) *Arch. Surg., Chicago*, **62,** 586.
McKeever, D. C. (1952) *J. Bone Jt. Surg.*, **34A,** 129.
Mith, R. N. (1952) *Brit. med. J.*, ii, 1385.
Thompson, F. R., and McElvenny, R. T. (1940) *J. Bone Jt. Surg.*, **22,** 555.

# Abduction Osteotomy as a Salvage Operation in Fracture of the Neck of the Femur

By A. J. HARROLD, F.R.C.S.
*London*

THE factors responsible for failure of union in fractures of the neck of the femur are not yet fully understood. With internal fixation failure results in about one-third of cases. We believe that the trouble often lies in the fact that blood shed into joints does not clot and become organized by granulation tissue as it does elsewhere. This paper relates our experience in trying to salvage these cases by abduction osteotomy of the femur.

Through angulation of the neck, the fracture site may be placed below the head so that the body weight no longer pushes the head downward past the fracture surface but directly against it. The conversion of shearing forces to impacting ones enhances immobilization of the fracture and encourages union. The operation may be contrasted with McMurray's osteotomy, which is a displacement osteotomy not an abduction one; by bringing the femoral shaft under the acetabulum it restores stability to the hip. With the abduction osteotomy, however, the same effect is obtained together with three further advantages—an increased chance of obtaining union of the fracture, a slight gain in leg length due to the vertical disposition of the neck, and thirdly a stretching of the abductors which helps to eliminate a Trendelenburg gait.

The technique is as follows: the anæsthetized patient is placed on the orthopædic table after manipulative reduction of any displacement present. The nail previously inserted is removed. The guide wire is placed more horizontally than usual, starting very close to the base of the great trochanter (Fig. 1). In calculating the length of the nail it is wise to leave at least 3/8 in. clearance between the tip of the nail and the hip-joint. The amount of abduction to be obtained is then assessed. We usually aim at an angle of about 40 degrees. A nail-plate is selected so that the angle between the shaft of the femur and the plate is about this amount. This demands a 150 degree or 160 degree nail-plate. After it has been driven home a wedge of bone with a 40 degree apex is removed. Preliminary drilling of the bone enables a clean osteotomy to be done. The lower margin of the wedge is best placed transverse to the line of the femur. The upper margin comes out just below the base of the nail. After removal of the wedge the plate together with the upper fragment is adducted on to the femoral shaft, the orthopædic table being adjusted to permit this, and a Loman's clamp is applied until the screws have been inserted.

The only special precaution taken afterwards is that we avoid passively adducting the leg. The patient lies free in bed, practising exercises, and is able to resume walking after eight weeks. In fact some of the more elderly patients may be allowed to sit out of bed long before this time.

We have done this operation in 23 patients in whom the fracture has redisplaced following primary nailing (Table I).

TABLE I

| | |
|---|---|
| Number of patients: .. .. .. .. | 21 female, 2 male |
| Age 39–83 .. .. .. .. .. | Average age 69 |
| Interval between fracture and osteotomy | |
| 12 days to 17 months .. .. .. .. | Average 11 weeks |
| RESULTS | |
| Further redisplacement .. .. .. (10 days to 15 months later) | 7 cases |
| Fracture united six months after osteotomy .. | 11 cases |
| Uncertain .. .. .. .. .. | 5 cases |

The assessment of results in fractures of the neck of the femur is notoriously difficult. What is certain in these patients is that in 7 complete redisplacement of the fracture has occurred. In 11, as judged clinically and radiologically at least six months from the operation, the fracture has united; 9 of these patients have been followed for over a year. In 5 the result is uncertain, either because the duration of follow-up is too short, or because although redisplacement has not occurred, radiographic union of the fracture is not present. Thus the fracture has probably united in over half the patients.



FIG. 1.



FIG. 2.



FIG. 3.

Fig. 2 is a reproduction of the radiograph in a successful case. Excellent function is usually associated with such appearances. If union has not been secured a tolerable functional result may still be obtained. A woman of 43 was still able to ski three years after her osteotomy when the radiographic appearances were as shown in Fig. 3. The hip hurts but is stable with no Trendelenburg dip. In the presence of severe pain a Girdlestone pseudarthrosis is probably the best treatment.

A relatively frequent occurrence has been penetration of the nail through the head from impaction and absorption at the fracture line. The tip of the nail may enter the hip-joint. We then prefer to shorten the nail rather than remove it completely. One or other operation has been necessary in 8 of the patients. Even when considerable absorption of the neck has occurred union may still be obtained.

This is a possible treatment for the "failed nail", the fractured neck of femur that has "fallen to bits" after internal fixation. It is technically easy and not a severe ordeal for the patient. The after-care is simple. Union of the fracture may be expected to follow in over half the cases. If union fails a reasonable palliation may be obtained. In the absence of a universally successful treatment for this condition abduction osteotomy deserves to be more widely known and used.

## Arterial Homografts in Injuries of the Extremities

By JÖRG BÖHLER, M.D.
*Linz, Austria*

FRESH traumatic ruptures of an artery endanger the injured limb. Therefore continuity of the vessel should be restored as soon as possible. End-to-end anastomosis is usually possible only after clean-cut trauma. In most cases the artery is torn by a blunt force and the arterial wall is damaged over a considerable length; therefore, after resection, direct suture is not possible because of tension. After traumatic rupture of an artery the results of direct suture are generally not satisfactory and deep-frozen or freeze-dried homografts should be used. We tried direct suture of a torn popliteal artery three times without success. In all 3 cases the site of the anastomosis clotted. Only since we began using arterial grafts have we successfully restored patent vessels and preserved limbs. In cases with extensive damage to the arterial wall, with or without clotting, we feel also that the artery should be resected and a homograft be substituted. We have not tried heteroplastic or alloplastic arterial grafts, because in the extremities the results are not satisfactory.

In addition to shock treatment with sufficient blood transfusions the following points should be observed:

(1) The operation should be performed without delay, if possible within the first eight hours, as after this time the chances for complete recovery diminish rapidly. However, restoration of arterial continuity should still be tried after eight hours because the limb can still be viable due to some collateral circulation.

(2) During the preparation for the operation arteriograms should be made to decide the exact level of the interruption.

(3) Operative exposure must be sufficient to recover both stumps and to provide ample space for the anastomoses. Flexion creases of joints should not be crossed by the incision at right angles.

(4) The artery must be resected until normal arterial walls are present on both stumps.

(5) In order to avoid additional damage to the circulation, the operation should not be performed under a tourniquet.

(6) During the operation heparin should be injected into the arterial stumps. Post-operatively no anticoagulants should be used because a hæmatoma will form with consequent infection. After infection thrombosis of the anastomosis is almost inevitable.

(7) Suture technique should be exact and as atraumatic as possible. Either silk No. 000000 or a 0·1 mm. plastic thread should be used. The type of suture seems not to be of major importance. Usually two everting mattress sutures and a running stitch are used. If possible the graft should be of the same calibre as the torn artery; otherwise the major artery should be narrowed by a wedge resection or the lesser artery cut obliquely.

(8) Around the anastomoses there should be no dead spaces in order to avoid hæmatoma formation.

(9) Strict asepsis and the use of post-operative antibiotics are important.

(10) If there is already ischæmia of the limb with swelling of the muscles, extensive fasciotomy should be performed.

(11) Concomitant fractures should be stabilized by osteosynthesis. In the shafts we use intramedullary nails and at the condyles either crossed wires or bolts and screws.

(This presentation was illustrated with an excellent film of arterial grafting in a case with rupture of the popliteal artery after a hyperextension fracture of the tibial plateau.)

# Section of General Practice

President—G. M. KERR, M.B., L.R.C.P., F.F.A.R.C.S.

[*February* 19, 1958]

## DISCUSSION ON EMERGENCIES IN GENERAL PRACTICE

**Dr. R. M. McGregor** (Hawick):

*Surgical Emergencies*

The family doctor is rarely called upon to undertake surgical procedures which are immediately life-saving in character; he is, however, called upon to make decisions and those practitioners associated with hospital beds are, in addition, expected to undertake a certain amount of useful surgery. I propose, therefore, to show the surgical cases I have encountered in the Cottage Hospital with which I am associated.

### OUT-PATIENTS

During the five years, 1952–1957, 477 patients were treated for conditions of a surgical nature. Table I shows them in their order of frequency. 10 of these cases were transferred to a larger hospital. The remainder were a personal responsibility.

TABLE I.—OUT-PATIENTS COTTAGE HOSPITAL 1952–1957

| Surgical (477) | | Transferred |
|---|---|---|
| Wounds | 90 | 3 |
| Fractures and dislocations | 77 | 5 |
| Sprains and strains | 75 | — |
| Septic conditions | 65 | — |
| Cysts and warts | 43 | — |
| Varicose conditions | 43 | — |
| Nasal conditions | 21 | — |
| Removal of foreign bodies | 15 | 1 |
| Joint conditions | 12 | — |
| Dental extractions | 12 | — |
| Burns and scalds | 10 | — |
| Gynæcological conditions | 7 | — |
| Urinary conditions | 6 | — |
| Appendicitis | 1 | 1 |
| | 477 | 10 |

Wounds of varying severity were the most common condition, and the hands and wrists (43 cases) were the regions most frequently involved. Wounds of the face were probably the most troublesome, since there was the need for a good æsthetic result. Sprains and strains (75 cases) can be the cause of prolonged invalidism. This is particularly evident when ligamentous structures of the shoulder-joint are severely damaged. The knee and ankle joints in the adipose and athletic individuals are also tardy of repair. The assurance given by a negative X-ray has frequently accelerated recovery. The outlook in septic conditions (65 cases) has been completely altered by the introduction of the sulphonamides and antibiotics. Strains resistant to penicillin have not been frequently encountered in this neighbourhood. This may be influenced by always using large doses when it is decided to administer penicillin. The early use of large doses immediately a finger becomes painful following the prick of a pin or needle, or when the breast of a nursing mother shows an area of localized tenderness, probably prevents more serious infection. The remainder of the conditions treated reflect a pleasure in doing odd jobs: the shelling out of sebaceous

cysts, the catching of a good crop of nasal polypi, and the removal of a variety of foreign bodies from every conceivable orifice give variety to a day's work.

A renewed interest in the injection treatment of varicose veins is shown by treating 63 cases. In these cases when a satisfactory clot is obtained the vein is opened and the clot expressed. This is followed by tight bandaging, and the hope is that recanalization will be prevented.

Table II shows the fractures and dislocations treated as out-patients. 5 of these cases were transferred to a larger hospital. It is understandable that upper limbs were in the majority when treatment was being given as out-patients.

TABLE II.—OUT-PATIENTS COTTAGE HOSPITAL 1952–1957

Fractures and Dislocations (77)

| Upper limbs | | Lower limbs | |
|---|---|---|---|
| Colles fracture | 28 | Potts fracture | 8 |
| Carpus and metacarpus | 16 | Tarsus and metatarsus | 3 |
| Humerus | 4 | Tibial shaft | 1 |
| Radius and ulna | 4 | Femur | 1 |
| Clavicle | 2 | Patella | 1 |
| Phalanges | 1 | | |
| Olecranon | 1 | | |
| | 56 | | 14 |
| Ribs | 3 | Dislocations | 4 |

IN-PATIENTS

Patients were admitted for observation and diagnosis as well as for treatment. The diagnosis was a personal responsibility but the treatment was often carried out by the visiting specialists. During the nine years, 1948–1957, 546 patients whose condition was of a surgical nature were admitted under my care. Table III shows these conditions in

TABLE III.—IN-PATIENTS COTTAGE HOSPITAL 1948–1947

| Surgical (546) | | Transferred |
|---|---|---|
| Orthopædic conditions | 117 | 13 |
| Gynæcological conditions | 114 | 0 |
| Ear, nose and throat conditions | 63 | 1 |
| Hernia and hydrocele | 42 | 0 |
| Septic conditions | 38 | 1 |
| Cancers | 33 | 12 |
| Varicose veins, ulcers and hæmorrhoids | 30 | 0 |
| Peptic ulcers | 28 | 3 |
| Genito-urinary diseases | 26 | 3 |
| Diseases of appendix, gall-bladder and pylorus | 23 | 3 |
| Cuts and bruises | 17 | 0 |
| Cysts, lipoma, bursæ, &c. | 8 | 0 |
| Dental extractions | 4 | 0 |
| Burns and scalds | 3 | 1 |
| | 546 | 37 |

order of frequency. Since orthopædic and gynæcological conditions top the list and contain most of the emergencies they are given in greater detail in Tables IV and V.

TABLE IV.—IN-PATIENTS (SURGICAL) COTTAGE HOSPITAL 1948–1957

Orthopædic conditions (117)

| Fractures: | | | | | |
|---|---|---|---|---|---|
| Upper limbs | | Head, neck and body | | Lower limbs | |
| Colles fracture | 18 | Skull | 8 | Potts fracture | 19 |
| Radius and ulna | 8 | Ribs | 4 | Femur | 13 |
| Humerus | 3 | Pelvis | 1 | Tarsal and metatarsal | 4 |
| Condyle avulsion | 1 | | | Tibia and fibula | 4 |
| | 30 | | 13 | | 40 |

| Dislocations: | | | |
|---|---|---|---|
| Elbow | 1 | Sprains and strains | 10 |
| Shoulder | 2 | Other orthopædic conditions | 21 |
| | 3 | | 31 |

TABLE V.—IN-PATIENTS COTTAGE HOSPITAL 1948–1957

Gynæcological Cases (114)

| Gynæcologist | | Own cases | |
|---|---|---|---|
| Uterine prolapse .. | 18 | Dilatation and curettage | 47 |
| Hysterectomy .. .. | 5 | Abortions .. .. | 24 |
| Ovarian cyst .. .. | 3 | Salpingography .. .. | 9 |
| Sterilization .. .. | 1 | Salpingitis .. .. | 1 |
| Gilliam operation .. | 1 | Removal of pessary .. | 1 |
| Perforated uterus .. | 1 | Antepartum hæmorrhage | 1 |
| Uterine polypi .. .. | 1 | | |
| Rectovaginal fistula .. | 1 | | |
| | 31 | | 83 |

The ear, nose and throat conditions are no longer the cause of urgent emergencies. There were 51 tonsillectomies performed by the visiting consultant. The septic conditions varied from infections of the hand to ischio-rectal abscesses. 3 cases were real emergencies since they were suffering from acute osteomyelitis. A high fever in a young person complaining of pain in a limb requires a blood culture. Pencillin should then be administered in large doses at frequent intervals without waiting for the result of the culture. The continuing of penicillin injections for some twenty-one days can be very trying for a young person. The cases of cancer were an exercise in diagnosis; some had already had treatment and were admitted because of the development of secondaries. Others received their operative treatment from the visiting surgeon. 12 were sent to a larger hospital because of the need of extensive surgery. The varicose conditions included 13 cases of hæmorrhoidectomy performed by the visiting surgeon.

The peptic ulcers included four patients with a localized perforation treated by conservative means. The 3 patients transferred were thought to need gastrectomy. 2 of the patients had severe hæmatemesis and were given blood transfusions. Among the genito-urinary conditions there were 10 cases of urethral caruncle in the female. This is a condition which is often overlooked as a cause of much discomfort in the female. They were all treated by the electrocautery. Diseases of the appendix were in the province of the visiting surgeon; 15 were interval appendicectomies. One case of pyloric stenosis required operative treatment. The cuts and bruises were conditions of some severity which I preferred to treat as in-patients, whilst the cysts, lipoma and bursæ indicate an enthusiasm for doing odd jobs. Burns and scalds were infrequent; one was very severe and was transferred for skin grafting after the initial shock was treated.

The visiting orthopædic surgeons do out-patient sessions only, but willingly give advice on any cases when one has elected to be responsible for the treatment. Table IV shows the 117 orthopædic cases treated in hospital. Of these 83 were fractures and the lower limb required more admissions owing to the difficulties of navigation. 10 of the cases of fracture of the femur were of the surgical neck. 21 of the orthopædic cases consisted of hammer toes, hallux valgus and exostosis which it gave pleasure to remove or rectify.

Table V shows the gynæcological conditions: 31 of these received their treatment from the visiting gynæcologist. The remainder were a personal responsibility. In 47 cases dilatation and curettage was carried out: in 3 for dysmenorrhœa, the remainder being cases of abnormal bleeding at the menopausal age. This was to ensure that no cancer was missed, and a cervical smear accompanied the uterine scrapings for pathological examination. No latent cancer was discovered in this series. The 24 cases of abortion probably caused the greatest anxiety among the emergencies. Here the giving of blood transfusions was the rule rather than the exception. The 9 cases of salpingography represent my interest in sterility. This measure is not only useful as a diagnostic measure but is also of therapeutic value. Of these 9 patients, 4 became pregnant and 5 healthy children have been produced.

These are the majority of the surgical conditions which have been encountered in one general practice. This paper may not add to medical knowledge but I hope that it does show that the family doctor still practises medicine and even performs some useful surgery.

**Dr. J. Guy Ollerenshaw** (Skipton):

*Medical Emergencies*

A medical emergency may be defined as "A medical situation which calls for the practitioner to take some immediate action at the time it is presented to him."

The recognition of a medical emergency in general practice depends on one or more of three reactions to some deviation from the normal.

These are (1) the reaction of the patient, (2) the reaction of the relatives, and (3) the reaction of the doctor.

The medical emergency which appears at hospital is one in which these reactions have already been sorted out and the case presented to the consultant is one to which the family doctor has reacted as a medical emergency of a particular type.

First let us dispose of the cases which fail to provoke any reaction of alarm in patient, relatives or doctor. For example a baby, apparently well only an hour or two earlier, is found dead in its cot. Post-mortem reveals an acute bronchiolitis which must have been in existence when it was last seen. Such cases, it may be said, belong to the pathologist and the coroner and do not come within our definition; but they are to us a salutary reminder that, far from being a dramatic event, a medical emergency can exist but be so quiet as to pass unnoticed.

At the other extreme is the emergency when the patient, relatives and doctor all recognize it as such: For example: a case of cardiac asthma where a woman rings up and says: "My husband has just come to bed and can't get his breath, he's asked me to send for you. Its awful, please come quickly." Here, patient, relative and doctor all agree that medical attention is required as soon as possible.

In type 1 it is only the patient who is reacting to the event as an emergency. A man rings up and says: "My wife says she is choking and insists that I call you. She doesn't look ill to me but she's all worked up and I'd be glad if you would call." He is not alarmed nor is the doctor who thinks of globus hystericus but it is an emergency to the patient who is demanding immediate action.

Not in all cases in this group does the emergency lie solely in the mind of the patient. Cerebral vascular accidents in known neurotics, for example, sometimes present in this way.

In type 2 the emergency lies in the mind of a relative, as when a simple urticaria almost closes a baby's eyes and a frightened mother calls for an immediate visit from an unperturbed doctor.

More rarely it is only the practitioner who is alarmed as in type 3. For example: A coronary thrombosis. "My husband said I hadn't to trouble you, doctor, but I thought you wouldn't mind telling me what to do. He's got an attack of wind and he doesn't seem able to shift it and he says his left arm aches." Here only the doctor realizes that a medical emergency exists.

To illustrate the three types, very simple examples have been chosen. Usually, of course, the assessment is much more difficult than this and the summons is compounded of two or more types in varying degree. Fortunately all three reactions are usually provoked in the emergencies which are most dangerous to life—poliomyelitis with paralysis, hæmoptyses and hæmatemeses and meningitis (a call to a case of severe headache and vomiting is the red light to most of us). In cerebral vascular catastrophes, epileptic fits, diabetic and insulin comas the patient plays no active part in asking for help but the doctor is usually informed that he is unconscious and this silent reaction does more to bring aid to him quickly than any vocal complaint he could make. The same may be said of the acute mental diseases where a sudden change in his behaviour pattern adds the touch of drama to the incoming call which assures it priority.

The reaction of the relatives is seldom absent but it may be muted when there is an epidemic raging which shows somewhat similar features. Indeed, so may be the reaction of the doctor and I wonder if some infamous poisoners would have been detected if they had waited until an epidemic of gastro-enteritis had been in full swing.

Unless the doctor himself answers the call the amount of anxiety in the mind of the caller is all that can be accurately assessed over the telephone. This is how the majority of emergency calls are first presented, though a trained secretary can ask simple questions which will elicit valuable objective evidence. Crude though it is, much depends on this assessment of the call. Errors of judgment at this early stage can result in dislocation of the doctor's work or, at worst, in delay in visiting an emergency, with consequences which may be grave. A second message coming within two hours of the first is usually an indication for hurry.

Occasionally serious medical emergencies present themselves at a routine surgery consultation and they are particularly important because they usually belong to type 3 where neither the patient nor his relatives have sounded the alarm.

Because the doctor is seeing the patient and not receiving a message from a third person it might be expected that recognition of an emergency would be simpler in these cases but,

in fact, this is often not so. The reasons for this are manifold but the predominating factor is the context in which they are seen—the busy routine surgery and a doctor whose alertness has been dulled by a succession of common-place disorders passing before him. There is a natural tendency, too, to think of one being sent for in an emergency and this sometimes results in a "blind spot" in dealing with patients in the consulting room where the emergency often presents in a quite undramatic way. The missed diagnosis is more often due to the doctor not having thought of that particular condition than to an absence of signs and symptoms which could have led to a correct diagnosis.

For a fuller explanation of the existence of this "blind spot" during surgery hours it is necessary to recognize how different is our approach to our cases from the methods we were taught in hospital. The number of patients to be seen makes impracticable the very complete history and examination which we were taught as students. Instead we tend to take a short history in the light of which several possible diagnoses suggest themselves. If examination with these diagnoses in mind is inconclusive a provisional diagnosis is made and the patient told to come up again. It is easy to condemn this method but most of us see no practicable alternative and the best we can do is to perfect it to the point where we can recognize the case which needs a more formal and systematic approach. It is true that we have always in mind the possibility of serious conditions presenting themselves in unexpected ways; and the chance of missing organic disease in the welter of symptoms produced by our neurotic patients is a constant fear; but we do at least have these possibilities in mind. The medical emergency, on the other hand, is a disorderly event which we do not associate with the general pattern of our surgeries and so it does not enter into the first differential diagnosis. A patient once died of his coronary thrombosis in my examination room. This event shocked me more because I was mentally unprepared for this sort of event in the course of a surgery than because of its tragic outcome. In this case the diagnosis was obvious and no treatment could be effective. Very different, however, was the case of a known psychoneurotic patient who passed through the consulting room as he had done many times before and straightway threw himself into the canal. The possibility of this being a medical emergency had not arisen during the consultation, but in the light of subsequent events it was thought that there were some clues in his demeanour and complaints which might conceivably have led to a correct assessment of emergency. Less dramatic but in my view a true emergency is the situation when a "neurotic" patient lets fall a remark which reveals or hints at the problem underlying his symptoms.

In the absence of his own doctor a man asked a partner for a repeat prescription of his stomach powder which he had been taking for his duodenal ulcer for several years. While writing the prescription the partner asked him if he had any idea what had brought on the pain on this occasion, specifically mentioning nervous stresses. These the man denied but as the doctor handed him the prescription he said "Well there's another thing I'd like to ask you about"; he then disclosed that sexual relations with his wife had been unsatisfactory throughout the nine years of married life.

The tranquillizer and an appointment to "come and see me to-morrow when I can spend more time with you" will not do in such a case; sufficient time has to be given to the case there and then to convince the patient that his trouble is at least understood and that hope of relief exists. Unless this has been done, to-morrow he may have regretted his impulse to confide and the doctor has lost his access to the problem.

The reaction of relatives serves a useful purpose in bringing help to the sufferer, but not infrequently it is in the nature of a second episode in a sort of chain reaction in which patient, relatives and doctor are all involved. The patient, seeing the concern of the relatives, often has the symptoms of anxiety or fear added to his original complaint—tachycardia, respiratory disturbance, sweating, and tense muscles simulating abdominal rigidity. Impressed by the resulting picture the general practitioner may remove the patient to hospital where these added symptoms disappear and the condition as presented in the ward is very different from that seen in the bedroom. However courteous the consultant's letter, when the patient is discharged next day, the practitioner feels slightly embarrassed if not positively humiliated. This illustrates the difference between medical emergencies in hospital and general practice. At the general practitioner level an emergency was present but the doctor had incorrectly evaluated the factors comprising it.

Any doctor who is satisfied to stop at treating the physical or mental condition which he has found in the patient is taking a far too narrow view of his functions and in a general practitioner to ignore the totality of the emergency is unpardonable. This I am sure was well understood by all general practitioners in the days when medicine was an art and science its very humble handmaid instead of the austere and slightly intimidating partner which it

is to-day. A rather fussy woman sent in the night on behalf of her husband, who was in pain. The doctor gave the immediate treatment and arranged for hospital admission next day. He then left the house rather abruptly. Later the wife complained bitterly to a partner. He was able to convince her that the doctor's treatment of her husband was correct but her sense of grievance remained. It was obvious that she was really complaining of the treatment meted out to her—or rather the lack of treatment. Her tension would have been relieved by a few words of explanation and reassurance about her husband but in his preoccupation with the patient the doctor had failed to do this.

The state of this woman's mind was part of the total emergency which existed and which it is our duty to recognize and treat.

This larger emergency is the reaction of other members of the family to an event which has suddenly shattered the pattern of home life. The father, instead of setting off to provide for the family, lies delirious upstairs, or the mother, instead of bustling round the house, lies moaning on the settee, or the child lies pale and unresponsive in its cot. The immediate reaction by the rest of the family is fear: for home has always been regarded as a secure haven in a rather frightening world. Even if it is not a very happy home it is to its members at the centre of things and its sudden disorganization leaves them lost and afraid. Because we know the cause of the disturbance—the patient's condition—and have some idea of what is likely to happen, we are in a better position than anyone else to start the process of adjustment to the new situation. Often, happily, we can give immediate reassurance that soon things will return to normal and that in the meantime such and such steps must be taken. But even when things are at their grimmest we can, from our experience, indicate how the situation can be dealt with. Once the mind is turned from helpless fear to constructive thinking the crisis is on its way to resolution.

The truth we seek is sometimes missed not because it is hidden at the bottom of a well but because, though out in the open, it stands alongside other truths which are so obvious that they get only a cursory glance. It is for this reason that this paper has directed attention to the following obvious truths:

(1) Emergencies can happen at any time in any place and to any person.

(2) In general practice a medical emergency presents not as a single problem, but as a complex, in which the part played by relatives may help to clarify or to obscure the central event.

(3) Serious organic disease is not a necessary component of a medical emergency in general practice.

(4) Treatment has to be directed not to the patient alone, but to the total situation which surrounds him.

# United Services Section

President—Sir CECIL WAKELEY, Bt., K.B.E., C.B., F.R.C.S.

[*March* 6, 1958]

## DISCUSSION ON INFLUENZA

**Major R. J. C. Hart, R.A.M.C. (London):**

*Virology*

The virus laboratory at the Royal Army Medical College was investigating outbreaks of influenza throughout 1957. The sources of positive findings during the year are shown in Fig. 1.

During the early part of the year there were a number of outbreaks due to the Dutch '56 strain of influenza virus A and one outbreak due to virus B. The Asian strain of virus A was first isolated in April from material sent to the College from cases in Hong Kong. While the virus was spreading through the Far East in the late spring and early summer, a number of outbreaks occurred on homeward bound troopships, and some of these landed cases in England. Apart from these, the first cases in the Army in the United Kingdom did not develop until early August when a number of units in Western Command suffered outbreaks. Further outbreaks occurred in rapid succession in other Home Commands and Germany, and somewhat irregularly in Middle East Command, Malta and Gibraltar.

Surgeon-Major Bulow will be describing his experiences with a large unit outbreak of influenza due to the Asian strain of virus A, Colonel Johnstone will discuss the complications, and Colonel Pace will deal with the epidemiology of the disease in Western Command.

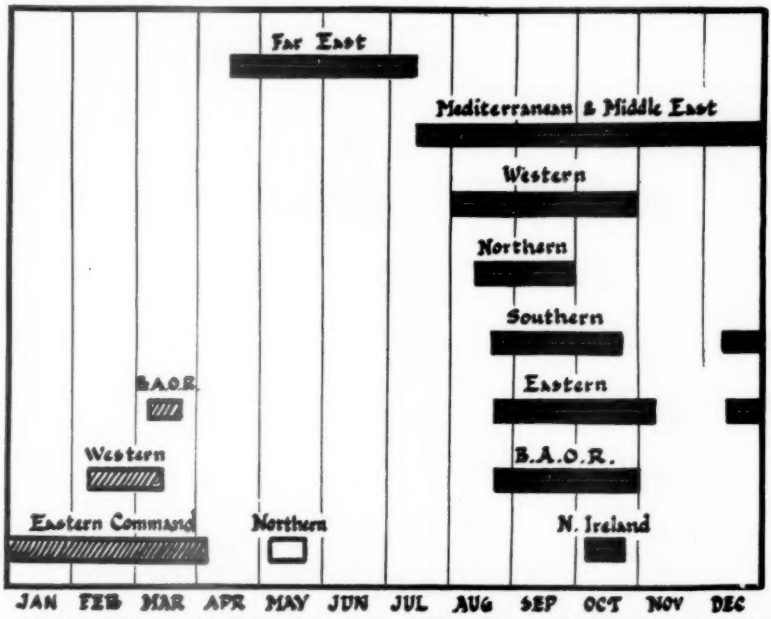



FIG. 1.—Incidence of influenza in the Army—1957. (From specimens examined in the Virus Laboratory, R.A.M. College.) Black=virus A (Asian), white=virus A (Dutch '56), hatched=virus B.

### VIROLOGICAL INVESTIGATIONS

Virus isolation was attempted as a rule from throat swabs. These are taken on wooden mounts, so that the head can be broken off into a ½ oz. bottle containing suitably buffered fluid (basic tissue culture medium is convenient and was usually used). The bottle is

then placed in solid $CO_2$ if obtainable, otherwise in ice, and sent to the Virus Laboratory by the fastest available transport. The advantages of this method over the use of gargling are that smaller numbers of specimens are toxic to eggs, and the containers are smaller, so that there is less difficulty in arranging for transport in ice.

The usual procedure was for up to a dozen of the earlier typical cases in an outbreak to be swabbed as soon as possible after the onset of the disease; cases occurring later in the outbreak were swabbed only if there was a reason, such as a second attack, very severe infection, or if it appeared that the outbreak, having died down, was starting up again.

Swabs were kept at −70° C. until required for investigation. They were then thawed, the fluid was withdrawn, antibiotics were added, and 0·1 ml. was inoculated amniotically into each of six 10-day-old fertile hens' eggs. After three further days' incubation, the amniotic fluid was harvested and hæmagglutinating activity against human and fowl red cells was examined as an indication of the presence of virus. If hæmagglutination occurred, an extract of the embryo was made by freezing and thawing, and tested by complement fixation against sera with known antibodies to influenza viruses A and B. The amniotic fluid harvested from negative eggs was inoculated into a further batch of eggs. A few of the isolations were made on the second passage, but most came up on the first. The positive amniotic fluids were inoculated allantoically into eggs to produce sufficient material for hæmagglutination-inhibition tests by which the viruses are typed. For this purpose, the allantoic fluid was sent to the World Influenza Centre, and it is a pleasure to acknowledge our indebtedness to Drs. C. H. Andrewes and A. Isaacs for typing our strains of influenza virus A.

The serological diagnosis of virus respiratory infections was made by complement-fixation tests. It is our practice to examine paired sera, one taken early in the disease and another taken usually in the third week. The second of these is "screened" by testing it at a dilution of $\frac{1}{8}$ with the following antigens: Influenza A, B, and C; Sendai; Adenovirus; Psittacosis; Q fever.

Positive findings on the screen test are investigated by titrating the pair of sera in doubling dilutions against the antigen concerned so that rising titres may be observed. A fourfold or greater rise is considered diagnostic. Negative antigen and saline controls are set up with each serum. During the period when "Asian flu" was at its height, this practice was varied by titrating all paired sera against influenza viruses A and B, and investigating other antibodies only if there was not a diagnostic rising titre to influenza. We were thus able to conserve our antigens and to examine all specimens sent in without delay. Had we continued "screening" we should have run out of certain antigens and there would have been a period of about four weeks during which we should not have been able to keep pace with the work coming in.

The serological diagnosis of influenza virus A infection was made in 1,196 cases and of influenza virus B in 31 during 1957. The monthly incidence of serological diagnosis of influenza virus A infection and of isolations of the virus is shown in Fig. 2. April marks the change-over from the Dutch '56 strain to the Asian '57 strain. Both isolations in April were due to the latter, and three serological positives came from the outbreak in Hong Kong from which the virus was isolated. The other four serological positives were from outbreaks in which the Dutch '56 virus was isolated. The serological positives in May were all from Hong Kong and it can be assumed that they were due to the Asian strain. In June and July a number of troopships arrived in this country from the Far and Middle East with reports of outbreaks of influenza on board. Most of these outbreaks had finished before the ships docked, and it was only possible to make a retrospective serological diagnosis. This was done by examining serum from a selection of cases. The selection was made by interviewing the Medical Officer on board and going through his records to find the days of maximum incidence of the disease and bleeding a convenient number of those reporting sick on those days without a history of other recent respiratory infections. As the titre to influenza virus A in the single convalescent specimens was high in all or nearly all of these cases it was assumed that the outbreak was due to influenza virus A. This occurred in all four troopship outbreaks investigated. Further studies to determine the strain responsible were not undertaken, as the Asian strain was known to be active in countries visited, and because the summer months are used in the laboratory to manufacture new batches of antigens for complement-fixation tests. These antigens might have been contaminated by the live virus required for hæmagglutination-inhibition tests.

In July troopships arrived with outbreaks in progress. The procedure used for the earlier ships was used to make a diagnosis the day after the ship docked, and the cases

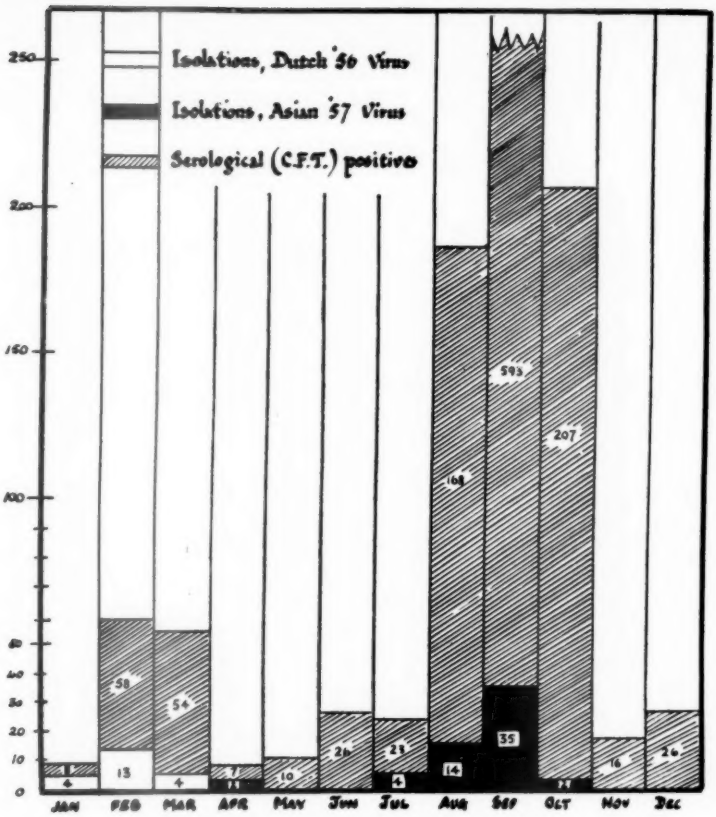



FIG. 2.—Positive findings—influenza A, 1957.

occurring during the three days before the ship arrived were swabbed for virus isolation and the first specimen of serum was taken. Follow-up letters enabled second specimens of serum to be taken from these men during disembarkation leave.

From early August, outbreaks of influenza A due to the Asian virus occurred in this country. Swabs and paired sera from the majority of outbreaks were examined in the virus laboratory. Not more than two isolations of virus were made from each outbreak, and usually only one. Owing to the fact that the bacteriology department was undergoing modernization, there was an acute shortage of incubator space and the number of eggs which could be accommodated was severely limited. This meant that there was an accumulation of specimens awaiting inoculation from the end of August, and the isolation of virus from outbreaks in September was not completed until December.

Serological diagnosis was not restricted, and complement-fixation tests were carried out on the day the specimen arrived in the laboratory or the day after. The proportion of cases in an outbreak which were so investigated depended on a number of factors. First specimens were taken from a number of cases which could not be traced for second specimens. Resources of some units were severely strained by the number of cases involved, particularly if there was an appreciable incidence of the disease among medical personnel, so that bleeding of large numbers of patients became impracticable. The cases occurring early in most outbreaks were bled whilst usually only a proportion of the later cases were investigated.

Fatal cases were usually examined *post mortem*, and lung or tracheal mucosa was sent for virus isolation, which was successful in 5 of the 9 cases from which material was examined.

Bacteriological examinations were made by the pathologist on the spot and at the College the results were identical, and are shown in Table I. It will be noticed that in 4 of the

TABLE I.—BACTERIOLOGICAL AND VIROLOGICAL INVESTIGATION OF FATAL CASES

| *Case* | Virus Isolated | Bacteriology |
|---|---|---|
| 1 | Influenza virus A (Asian) | *Staph. aureus* (resistant) |
| 2 | Influenza virus A (Asian) | — |
| 3 | Influenza virus A (Asian) | — |
| 4 | None | *Staph. aureus* (sensitive)<br>*Strep. pyogenes* (group A) |
| 5 | Influenza virus A (Asian) | *Staph. aureus* (resistant) |
| 6 | None | *Staph. aureus* (sensitive) |
| 7 | None | *Staph. aureus* (resistant) |
| 8 | Influenza virus A (Asian) | — |
| 9 | Not examined | *Staph. aureus* (resistant) |
| 10 | None | — |

6 cases from which *Staphylococcus aureus* was isolated, this organism was resistant to penicillin. This may have some bearing on the question of the origin of the strain—do the patients bring their staphylococci with them or do they acquire them in hospital? If the latter is the case, it is another indication of the danger of hospitalization. Further information is required in order that the relative importance of the influenza virus and bacteria, particularly staphylococci, can be assessed in fatal cases.

**Surgeon-Major G. H. Bulow,** The Life Guards (Windsor):

Last autumn I had the opportunity as a Unit medical officer of studying a small outbreak of influenza. Although it was a *small* outbreak in a relatively *small* community at risk, the advantages of being able to follow up every case far outweighed this disadvantage. And although my short study does not reveal any new dramatic observations it does go some way to confirm a few of the facts that have been mentioned in recently reported series.

The outbreak studied concerned personnel in Windsor from three main Units:

| | | | |
|---|---|---|---|
| The Life Guards .. .. .. .. | Approx. strength | 600 | Total 1,700 |
| 2nd Bn. Grenadier Guards .. .. | Approx. strength | 700 | |
| Household Cavalry Training Squadron .. | Approx. strength | 400 | |

The outbreak commenced suddenly on September 7, 1957, and lasted for six weeks: 297 cases were admitted to The Household Cavalry Hospital and studied in detail. It was estimated that a further 100 cases from the garrison had influenza whilst on leave. Thus the attack rate within the garrison during this short epidemic was approximately 23·5%.

## EPIDEMIOLOGY

In early September 1957 the influenza epidemic was well established in the North of England and there had only been relatively few cases in the civil population of Windsor.

The Medical Officer of Health for Windsor had been warned that the influenza epidemic was spreading South but clear evidence of it in Windsor did not appear until the second or third week in September. The first evidence of any mass involvement appeared in the school children, chiefly affecting those between 9 to 13 years. Within a week the infection had spread to all age groups in the children and he estimated that almost 50% of the school population probably suffered from influenza. There then appeared to be a slight lull of about three weeks before the peak of the infection was reached in the adults, but a much smaller proportion of the population was affected, estimated at about 20% to 25%.

4 of the first 5 Service cases in this series who were admitted to hospital had travelled to Windsor from the North within the previous twenty-four hours on September 6 and 7, 1957.

All further cases admitted had remained in the Windsor area except for a few who had moved about in the South of England and 4 others who returned from leave: Case 23 from Stoke-on-Trent, Case 30 from Warwick, Case 40 from Liverpool and Case 145 from York.

Spread of the epidemic within the garrison consisted of small explosive outbreaks in squadrons, squads and barrack rooms. The attack rate in a barrack room was frequently well above the overall attack rate of 23·5%. This was especially noticeable in the young recruits who were housed in rather cramped conditions due to rebuilding, and who spent much of their spare time in their rooms cleaning and sorting their kit, uniform, &c.

## CLINICAL FEATURES

All cases were seen within twenty-four hours of the onset of symptoms. Typically the patient was a young male (all except 3 were aged between 15 and 30 years) who complained of a sudden onset of headache, dry cough, aching eyes and generalized body pains. The

conjunctivæ were often injected and the tongue coated. The temperature was usually over 100° F. often with a relative bradycardia.

Clinical manifestations among the 297 patients admitted were as follows:

| | % | | % |
|---|---|---|---|
| Headache .. .. | 80·1 | Conjunctival injection | 21·9 |
| Pyrexia over 100° F. | 79·9 | Retro-orbital pain .. | 23·3 |
| Aches and pains .. | 50·5 | Prodromal coryza .. | 14·5 |
| Cough .. .. | 49·5 | Retrosternal pain .. | 13·1 |
| Sore throat .. .. | 38·4 | Nausea and vomiting | 7·7 |
| Coated tongue .. | 30·9 | | |

Treatment was symptomatic. The average duration of pyrexia was 2·5 days. The average time in hospital was 6·2 days after which the patient usually returned to full duty.

Investigations made included paired sera from 258 patients. 2 of these were negative and the remainder positive to influenza-A virus. A batch of throat swabs was taken from which the Asian strain of virus was duly isolated.

Complications were few and of minor nature : there were 3 cases of bronchitis ; 2 of otitis media; and one case of pneumonia.

The course of the disease was one of rapid improvement with very few exceptions: 14 cases developed herpes labialis; 6 had a prolonged cough (over a week); 4 had a prolonged pyrexia (over a week); and 4 cases developed epistaxis (no previous history).

### Discussion

The clinical features and epidemiological effects reported compare in most instances with previous reported series (Holland, 1957; Guthrie *et al.*, 1957, Fry, 1958). It was a very widespread infection affecting predominantly young persons but of a very low degree of virulence. The attack rate was much higher in the younger men especially where these were living in rather crowded barrack rooms. As many as 70% of the inmates of one barrack room were admitted within two days of each other. The number of cases occurring in the outbreak from its onset on September 7, 1957, rose steadily to the end of the fourth week and completely subsided by the end of the sixth week. One case (No. 97) had a clinical recurrence after ten days but serological investigations only confirmed his first attack as due to influenza-A virus.

### REFERENCES

Fry, J. (1958) *Brit. med. J.*, i, 259.
Guthrie, J., Forsyth, D. M., and Montgomery, H. (1957) *Lancet*, ii, 590.
Holland, W. W. (1957) *Lancet*, ii, 840.

**Lieutenant-Colonel R. M. Johnstone, M.B.E., M.C., R.A.M.C.** (London):

*Complications Seen in Patients with Influenza*

My remarks are based upon data collected for me by Dr. Christopher Blagg from approximately 1,060 cases admitted to the Cambridge Military Hospital, Aldershot, during the period August to November 1957. The complications seen may be divided into those affecting the respiratory systems and those affecting other systems.

To take the latter first, concussion occurred in a few patients who fainted on parade during the prodromal period. Vomiting, diarrhœa and abdominal pain also occurred. The importance of abdominal pain lay in the fact that during the early stages of the outbreak such cases tended to be admitted to the surgical wards and at least one patient underwent appendicectomy.

In the respiratory system, starting from the top, epistaxis was quite common but only one case needed treatment for this symptom. There were a few cases of sinusitis and tonsillitis. Tracheo-bronchitis occurred especially in those who gave a previous history of being "chesty". Two types of pneumonia were seen: staphylococcal and influenzal. The patients with staphylococcal pneumonia fell into three groups:

(*a*) Those who responded well and quickly to antibiotics and gave us no trouble.

(*b*) Those who had signs and symptoms of respiratory obstruction due to blocking of the bronchi with plugs of tenacious mucus.

(*c*) Those who developed peripheral circulatory failure, which differed in no way from what one has seen previously in other severe staphylococcal infections. One such patient died.

Post-influenzal pneumonia was seen in 2 patients and was characterized by gross cyanosis and air hunger and death from anoxæmia. At post-mortem the lungs of both patients were completely sodden with œdema. There were a few pinhead abscesses from which staphylococci were cultured but I am sure they played no part in the cause of death. We found that during the early stage of the disease neither of these 2 patients had had adequate rest and it may be that this was a factor in allowing the development of pneumonia.

Syn-pneumonic pleural effusions occurred and in one case went on to the development of a staphylococcal empyema which ultimately required surgical drainage. Recently one case of collapse of a lower lobe following influenza has passed through our hands at the Queen Alexandra Hospital, Millbank.

*Treatment.*—Most cases received only symptomatic therapy. When signs developed in the chest, penicillin and streptomycin were given and erythromycin was held in reserve until the results of cultures were known. In those cases of staphylococcal pneumonia with peripheral circulatory failure, a glucose saline drip was set up and hydrocortisone, noradrenaline and erythromycin were given through the drip. In those cases with signs of respiratory obstruction, treatment was directed to maintaining a clear airway by postural drainage and bronchoscopy. Cortisone was not used as a routine, but in retrospect it appears possible that its anti-inflammatory action might have been helpful in the 2 cases of post-influenzal pneumonia.

**Colonel T. A. Pace, O.B.E., M.D., B.Sc., D.P.H.** (Chester):

*Asian Influenza in Western Command*—1957

This account deals mainly with the widespread epidemic of Asian influenza in the Command during late summer and early autumn 1957. The total strength of the Command is approximately 29,000 troops.

The epidemic lasted during the twelve weeks from August 12 to November 3, with approximately 100 outbreaks. Every unit was affected. Total notifications numbered 5,277 (overall attack rate 17·3%); this figure does not include those who reported sick while on leave from unit (Table I). The first outbreak occurred at Long Marston during the week

TABLE I.—WESTERN COMMAND. ASIAN INFLUENZA—1957

I. NEW CASES OF INFLUENZA

| Week ending | North West District | Mid West District | Total |
|---|---|---|---|
| Aug. 18 | 7 | 57 | 64 |
| 25 | 14 | 53 | 67 |
| Sept. 1 | 21 | 165 | 186 |
| 8 | 48 | 217 | 265 |
| 15 | 165 | 262 | 427 |
| 22 | 379 | 630 | 1,009 |
| 29 | 300 | 922 | 1,222 |
| Oct. 6 | 168 | 800 | 968 |
| 13 | 104 | 419 | 523 |
| 20 | 76 | 243 | 319 |
| 27 | 31 | 120 | 151 |
| Nov. 3 | 7 | 69 | 76 |
| Total | 1,320 | 3,957 | 5,277 |

II. INFLUENZA DEATHS—ENGLAND AND WALES (GREAT TOWNS) (REGISTRAR-GENERAL)

| Week Ending | |
|---|---|
| Sept. 14 | 47 |
| 21 | 121 |
| 28 | 282 |
| Oct. 5 | 442 |
| 12 | 591 |
| 19 | 600 |
| 26 | 396 |
| Nov. 2 | 263 |
| 9 | 149 |
| 16 | 102 |
| 23 | 70 |

ending August 18. By the end of August Ashton-under-Lyne, Preston, Chester, Donnington, Brecon, Rhyl and Wrexham were involved. There was a gradual increase in incidence during the first five weeks, then a sharp rise with the peak incidence in the seventh week (ending September 29). A rapid decline followed, and the epidemic was virtually over by the end of the twelfth week. Virus A/Asian/57 was isolated from outbreaks in Preston, Chester, Donnington, Long Marston, Rhyl, Wrexham, Brecon, Cardiff and Manorbier.

### CLINICAL PICTURE

The majority of cases were mild, responded to symptomatic treatment, and were fit for duty within seven days of onset. Complications were few. There were only 3 deaths, of which 2 were due to staphylococcal pneumonia, and 1 due to purulent pleural effusion and brain abscess. The infecting organism in each case was *Staph. aureus* (coagulase positive).

### NOTIFICATION

In November 1956 the Ministry of Health (1956) scheme of "ascertainment" of winter epidemics was adopted in Western Command. Unit medical officers and medical officers at Chester Military Hospital and at the various Medical Reception Stations were nominated "spotters", while the Assistant Director of Medical Services of each District was to be the focal point through whom all epidemiological information would be channelled to the Ministry of Health (SMO 3) after due liaison with the local Medical Officer of Health.

In June 1957 all medical officers in the Command were warned of the possibility of an outbreak of influenza. Early in July they were instructed to submit a brief report as soon as an outbreak was established, giving the salient features. We were thus well prepared by the time the epidemic broke out in August. A modified system of notification was

immediately introduced, whereby unit medical officers notified daily to their A.D.M.S. by 'phone the total number of new cases that had occurred during the previous twenty-four hours. The A.D.M.S. then telephoned to the D.D.M.S. at Command Headquarters the daily total for their District. It is considered that a high degree of accuracy of notifications was achieved, as can be deduced from the remarkable similarity of the District incidence graphs not only to each other but also to the graph showing the number of deaths from influenza—England and Wales (*see* Table I).

## Epidemiology

Every Unit was involved in the epidemic. Attack rates varied from 3·5% to 48%, with an overall Command incidence of 17·3%. Proportionately the incidence among officers was very low compared with that of the rank and file. Table II gives an analysis of all the

Table II.—Western Command. Asian Influenza Epidemic August 11 to November 3, 1957. Analysis of Outbreaks in Units with an Average Strength of 100 or More

| Serial | Type of Unit | Aver. strength | Number of outbreaks by attack rates (%) 1– | 5– | 10– | 15– | 20– | 25– | 30– | 35–39 | 48·8 | Total outbreaks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Direct Intake Units: | | | | | | | | | | | |
| | (*a*) R.A. Sel. Regt. | 732 | | | | | 1 | | | | | 1 |
| | (*b*) R.E. Trg. Regt. | 793 | | | | 1 | | | | | | 1 |
| | (*c*) Infantry Depots | 254 | | | | 3 | 5 | 7 | 1 | | | 16 |
| | (*d*) R.P.C. Depot.. | 1,129 | | | | | | | 1 | | | 1 |
| 2 | Schools of Instruction: | | | | | | | | | | | |
| | (*a*) Officer Cadets | 520 | | | | | | | | 1 | | 1 |
| | (*b*) Apprentices .. | 1,010 | | | | | | | | | 1 | 1 |
| | (*c*) Anti-Aircraft | 642 | | | 1 | | | | | | | 1 |
| 3 | R.A. Units (other than Ser. 1a): | | | | | | | | | | | |
| | (*a*) Training Regts. | 822 | | | 2 | | 1 | | 1 | | | 4 |
| | (*b*) Field Units .. | 506 | | 2 | 2 | | | 1 | | | | 5 |
| | (*c*) Junior Leaders Regiment .. | 478 | | | | | 1 | | | | | 1 |
| 4 | Infantry Battalions | 500 | | 1 | 1 | 1 | | | | | | 3 |
| 5 | R.A.S.C. Companies | 152 | 2 | | 1 | 1 | | | | | | 4 |
| 6 | Static Units: .. | | | | | | | | | | | |
| | (*a*) Formation H.Q. | 151 | 1 | 2 | | | | | | | | 3 |
| | (*b*) Depot Regt. R. Signals .. | 824 | | 1 | | | | | | | | 1 |
| | (*c*) R.E. .. .. | 737 | | | | | | | 1 | | | 1 |
| | (*d*) Military Hosp. | 318 | | 1 | | | | | | | | 1 |
| | (*e*) R.A.O.C. .. | 1,307 | | 2 | | 1 | | | | | | 3 |
| | (*f*) R.E.M.E. .. | 187 | | 1 | 1 | | | | 2 | | | 4 |
| | (*g*) R.A.P.C. .. | 385 | | | 2 | | | | | | | 2 |
| | Total outbreaks | | 3 | 10 | 10 | 7 | 8 | 8 | 6 | 1 | 1 | 54 |

outbreaks which occurred in the 54 Units where the average strength was 100 or more. One outbreak occurred in each of these units. The majority of attack rates were spread evenly over a range varying from 5% to 34%.

The majority of Direct Intake Units had an incidence higher than the average. These units receive a regular flow of recruits direct from civilian life, and new foci of infection were therefore being constantly introduced. The high incidence in the Army Apprentice School, Chepstow, was due to a number of factors:

(*a*) The school reassembled after the holidays on August 17, thus bringing boys together from all over Britain.

(*b*) The apprentices are in their late teens (average age 16) and therefore highly vulnerable.

(*c*) There was a high incidence of influenza among the population of near-by Chepstow.

Apart from this, however, there was no apparent relationship between the size of an outbreak and the location or type of Unit, or the standards of living accommodation.

(*a*) Officer Cadet School, Chester, and School of Anti-Aircraft Artillery, Manorbier. Both schools receive a regular intake of students from different units in Britain, but the attack rates were 36·5% and 11·5% respectively.

(*b*) Depot Regiment, Royal Signals, Saighton Camp, near Chester. This is a transit camp for personnel on their way to or from overseas, but in spite of this constant flow of new arrivals from widely scattered areas both at home and abroad, the attack rate was only 7·8%.

(*c*) Depot Cheshire Regiment, near Chester, and R.A.P.C., Ashton-under-Lyne. The former occupy modern permanent barracks completed in 1940, while the latter live in hutted accommodation of extremely poor standard, but the attack rates were 28% and 13·9% respectively. Similarly the male staff at Chester Military Hospital occupy hutted accommodation of a very poor standard, but had an even lower attack rate (7·9%).

(*d*) The incidence among the three Infantry Battalions employed on garrison duties varied from 9·2% in 1/Welch at Worcester to 19·7% in 1/Manchester at Formby.

(*e*) In the four R.A.S.C. Companies where the men are all employed as drivers, the incidence varied from 3·5% (12 Coy at The Dale, Chester) to 15·6% (64 Coy, Preston).

There was no evidence of direct spread from billet to billet. The outbreak usually started simultaneously in different billets of the same barracks or camp. The attack rates in individual billets were approximately the same. As usual, mild cases who remained ambulant must have been a contributory cause of the spread of infection.

### Management of Cases

The number of cases admitted to a medical unit (hospital or medical reception station) was 2,627, or 49·8% of the total. The majority of admissions (85·3%) were to Medical Reception Stations.

The remainder were treated in barrack rooms or billets specially earmarked for sick accommodation, the main requirements being easy access to the unit cook-house and adequate ablution and latrine facilities in the same block. Unit fatigue parties were responsible for collecting food, serving meals and keeping the room clean. Cases were kept under careful medical observation, and those with early signs of lung involvement were immediately transferred to hospital (as distinct from a Medical Reception Station). While nursing was not up to ideal hospital standards, no untoward incidents occurred, and the arrangements were an ideal compromise between flooding out hospitals with comparatively mild cases of a short duration and letting patients bed down in their own beds scattered all over unit lines.

The Officer Commanding, Western Command Laboratory, kept constant liaison with the Unit Medical Officers, with the result that samples for laboratory examination were submitted from the majority of outbreaks.

### Preventive Measures

With the disease so widespread limitation of movement of personnel was not considered practicable or advisable, since nothing short of strict quarantine would have been effective. Measures were limited to:

(*a*) Adequate bed spacing. (*b*) Adequate ventilation of barrack rooms. (*c*) Proper washing and sterilization of cutlery and crockery. (*d*) No dry sweeping or shaking of blankets in barrack rooms. (*e*) Advice by the unit medical officers on the use of handkerchiefs for coughing and sneezing, and on keeping away from crowded places like cinemas, etc., in towns with a high incidence of influenza.

None of the cases had been inoculated with influenza vaccine.

### Asian Influenza in I.N.S. *Mysore*

Asian influenza broke out on August 25, 1957, in the Indian cruiser I.N.S. *Mysore*, berthed at Birkenhead. A total of 202 cases, representing an attack rate of 26%, occurred during the period August 25–September 10, the peak incidence (33 cases) being on September 5. Virus A/Asian/57 was isolated from one of the cases.

The short duration of the epidemic was due no doubt to the confined living conditions of the mess decks which are inevitable in a cruiser. Out of 17 mess decks, 15 were involved in the outbreak. The only mess decks which remained free had comparatively little overcrowding. The number of cases admitted to hospital was 194. This was necessitated not so much by the clinical condition of the patients (all cases were of a very mild nature) but by the cramped conditions on board which made nursing impracticable.

### REFERENCE

Ministry of Health (1956) *Mon. Bull. Minist. Hlth. Lab. Serv.*, **15**, 226.

# Section of Ophthalmology

President—J. R. WHEELER, F.R.C.S.Ed.

[*February* 13, 1958]

## Functional Spasm of Accommodation [*Summary*]

By L. H. SAVIN, M.D., M.S., M.R.C.P., F.R.C.S.

*London*

FUNCTIONAL spasm of accommodation was described by von Graefe in 1856. Cases are relatively infrequent and difficult to follow up in hospital practice. This paper is based on a series of 12 private patients who between them suffered from 21 recorded attacks of the condition. The diagnosis of the refractive error was made subjectively, and then confirmed by repeating the refraction after paralysis of the accommodation with atropine or homatropine. Cases with more serious symptoms were in males, though actually there were 8 females in the series as against 4 males. The condition was restricted to age groups with active accommodation, 3 under 10 years, 4 in the second decade, 2 in the third, 3 in the fourth decade at the time of the initial attacks. 5 patients were hypermetropic, 3 emmetropic, and 4 myopic under full cycloplegia. Myopes seemed to suffer worse spasms than the others. The degree of spasm achieved as much as 8 dioptres in the worst cases, more commonly 3–5 dioptres.

The commonest complaint was that of difficulty in distant vision. 7 of the 12 cases had associated frontal headache, not of very severe degree. Most cases showed distance esophoria and sometimes diplopia during an attack. There was, however, a minority of cases where the muscle balance readings showed exophoria.

Associated mental stress was noted in no less than 10 of the 12 cases, and it was undoubtedly the precipitating factor in most cases. The typical emotional situation was either simple fright or one in which an ambitious but rather inadequate personality was attempting a task just a little too hard, in which failure would entail "loss of face". Typical cases included a small boy not quite up to the standard of a scholarship he was attempting, and an ex-grocer's boy who was determined to become a certificated teacher.

Almost any treatment proves successful which will tide over the precipitating crisis without puncturing the balloon of the patient's self-esteem. Atropinization will work provided it is carried past such critical dates as those of approaching examinations. Treatment by orthoptics helps indirectly, largely because of the sympathy shown by kind-hearted orthoptists. Simple reassurance and advice will usually cure individual attacks, though it is difficult to alter personality and attacks tend to recur.

## The Use of Pilocarpine in the Treatment of Squints

By JOHN WHITWELL, F.R.C.S., D.O.

*London*

IT is intended in this paper to discuss the theory of the use of pilocarpine in the treatment of squints. In the development of binocular vision, the eyes become linked together by a set of physiological reactions known as the binocular reflexes. The phylogenetically ancient ones are unconditioned reflexes, but the more recent ones in development, such as fusion and stereoscopic vision, are conditioned and will require constant practice and reinforcement to become efficient. During the early years of training, some obstacle, often light, is liable to tip the scales against binocular vision and produce a squint. The majority of squints are of an accommodational nature and the commonest obstacle is hypermetropia.

Accommodation and convergence are closely associated in the accommodation-convergence reflex, which is divided up into three components:

(1) The *occipital convergence reflex* is the basic linkage between accommodation and convergence, closely associating the two functions in degree.

(2) The *harmonic accommodation reflex* is a later development and allows a certain amount of latitude between the two functions. Thus an overcorrected myope need not squint and a visually normal adult can tolerate small base-out prisms without blurring distance vision. It is this reflex that accounts for the fact that so few hypermetropes actually squint.

(3) The frontal accommodation reflex admits the ability of the individual to exert a voluntary conscious effort on either of the two functions.

A typical candidate for convergent squint is aged about 2½ years. His foveal central vision is not fully developed and the degree of fusion is limited. He is long-sighted but unfortunately the ciliary muscle is still not fully developed. There are, therefore, two defects of accommodation: a static defect—his hypermetropia, and a dynamic defect—maldevelopment of his ciliary muscle. In addition, numerous childish ailments are liable to include the ciliary muscle in the general debility, thus adding to the dynamic defect. The child is often mentally bright, taking a precocious interest in his surroundings. The two defects of accommodation infuriate the child, the frontal accommodation reflex is used to boost up the accommodation, the harmonic reflex is not yet able to control the esophoria, which breaks down to become a convergent squint.

We thus get the typical history of the long-sighted child, maybe recovering from whooping cough or measles, often tired at the end of the day, turning in one eye when he is trying to feed himself or kissing his mother goodnight. The habit of squinting has begun and all bad habits are easily picked up at this age. The occasional squint for near can soon become the constant squint for near, and then constant for all distances. When binocular distance vision is retained, the squint is eminently treatable, even though the overconvergence, once it has become a habit, can persist after the fullest possible spectacle correction.



FIG. 1.—F., aged 7, with a fully accommodative squint. Refraction each eye +2·0 D.S./+1·0 cyl, 90 degrees. The second photograph shows the squint fully controlled on pilocarpine treatment, even without glasses.

Similarly, an overconvergence for near may persist after the operative treatment of squint even after a full 5 mm. bilateral recession of the medial recti. As most orthoptic treatment such as bar reading, is done at near distance, this is a considerable obstacle.

For this condition, bifocals are sometimes ordered but are usually ineffective because the child rarely looks through the reading segment. Some surgeons atropinize the eyes, but although atropine paralyses the accommodation it does not paralyse the will to accommodate. An interested child will squint violently in an effort to overcome his weakened accommodation. A miotic fixes the accommodation for near without any nervous intervention and thus dispenses as much as possible with the frontal accommodation reflex (Javal 1896; Abraham, 1949, 1952; Whitwell and Preston, 1956). Pilocarpine seems to be the most useful drug and the usual starting dose is the 1% guttæ t.i.d. to both eyes. This level of dosage is maintained for at least a month, but is continued until a less frequent application

controls the squint, and then the treatment is gradually withdrawn. The advice of the orthoptist in charge of the case is invaluable in regulating the dose. If the treatment is going to be successful it will be apparent after the first or second drop, and it is useless to prolong treatment beyond this if the squint is not controlled.

Pilocarpine has a beneficial effect on fully accommodative squints in three ways. Firstly, by locally setting the accommodation for near, the frontal reflex is not brought into use. Secondly, the associated miosis, by providing a far greater depth of focus, makes it unnecessary for the child to exercise as much accommodative effort to get a clear close image. A third possible factor is that the constant spasm of the ciliary muscle causes the muscle to strengthen and hypertrophy. This would tend to remedy one of the principal original causes of the squint, namely, a dynamic defect of the accommodation.

One criticism that can be very legitimately levelled against pilocarpine is that it must blur the distance vision. It certainly does blur it a little, but not to any great extent. Possibly the miosis keeps it to a minimum. But, in any case, our main problem is with near vision, where we must break the squinting habit. It might be supposed that D.F.P. solution would be a more convenient miotic, as once daily instillation would be sufficient. D.F.P. is a very strong miotic and there is no residual accommodation after its use. With pilocarpine, there is usually a dioptre or two of accommodation left, which the orthoptist finds beneficial. The twenty-four hours activity of D.F.P. is a disadvantage in the "weaning" stages, for then the child may only need two hours' help at the end of the day. An intelligent child will come and ask for a drop when he is beginning to be troubled by diplopia.

The cases likely to be benefited by pilocarpine are of two types. Firstly, the post-operative condition, with binocular vision for distance and a residual convergent squint for near. Secondly, the fully accommodative squint (Fig. 1). Also, although I have had no opportunity to try it, the treatment might well be useful in cases of emergency, where a quick refraction is not possible. A circumstance that comes to mind is that of a child confined to bed with illness, who is beginning to squint. However, full stereoscopic vision must be present. When this is absent only a temporary reduction in the angle is achieved. Also, the angle of squint must not be too large, although there is no definite limiting angle. An accommodational squint with a Maddox Wing reading of +30 degrees has been controlled, but the usual successful cases have a Wing reading of between 10 degrees and 20 degrees. It is often quite surprising how little the Wing reading sometimes has to be reduced to allow the squint to be controlled.

In conclusion, pilocarpine in properly selected cases can be of real assistance to the orthoptist in treating the convergence excess type of squint.

REFERENCES

ABRAHAM, S. W. (1949) *Amer. J. Ophthal.*, **32**, 233.
—— (1952) *Amer. J. Ophthal.*, **35**, 1191.
JAVAL, E. (1896) Manuel du strabisme. Paris; pp. 45, 81.
WHITWELL, J., and PRESTON, A. (1956) *Brit. J. Ophthal.*, **40**, 96.

## Orthoptic Treatment of Accommodative Convergent Strabismus

By SHEILA MAYOU, D.B.O.(T.)
*London*

THIS paper is concerned with the treatment of accommodative convergent squints. It does not deal with those convergent squints which merely have an accommodative element.

The age of onset of an accommodative convergent squint varies between 2 to 4 years. Most of the patients have a simple hypermetropic correction, which rarely exceeds + 6·00 D.sph. But some are emmetropic.

Many can be successfully cured by orthoptic treatment alone; others, particularly adults, require operation, in which case the orthoptic treatment is basically post-operative. In all cases, the objective is to obtain a good standard of binocular visual acuity for distance and near. Normally, this standard will be 6/5 and N5 with correction and the same without correction provided that the manifest hypermetropia did not exceed +4·00 D.sph.

The first and essential prerequisite to orthoptic investigation and treatment is of course an examination of the fundi and media and refraction. If refraction shows that the patient needs correction, the diagnosis of the type of squint and its preliminary classification should not be made until the correction has been worn for at least a fortnight. Moreover, on examination, most of these patients will be found to be amblyopic and it is unwise to make

the orthoptic diagnosis until the amblyopia has been overcome. In some cases, the vision in the amblyopic eye may be as low as 6/36, compared with 6/9 in the good eye. In others the amblyopic eye may be 6/12 and the good eye 6/5 or even 6/4. The point is that in all these amblyopic cases the visual acuity of the amblyopic eye must be brought up to the standard of the good eye which, in turn, sets the standard for the binocular visual acuity. The visual acuity of both eyes must therefore be accurately measured at an early stage; but the first test rarely reveals the full vision of the good eye.

Once any amblyopia has been overcome, the patient should fall within one of three categories:

The first consists of the fully-accommodative convergent squints. Patients in this category are binocular with correction for distance to 6/6 or 6/5 and for near to N 5 but have a manifest deviation for all distances without correction.

The second consists of the accommodative convergent squints with convergent excess. Patients in this category are binocular for distance to 6/6 or 6/5 but have a convergence excess for near in correction and a manifest deviation at all distances without correction.

The third category is the same as the second but with emmetropia. Here the patients are binocular for distance to 6/6 or 6/5 and have a convergence excess for near.

Although a patient in any of these categories usually has normal binocular visual acuity for distance in correction, this may deteriorate as a result of illness or stress and give rise to an occasional manifest deviation, in which case the binocular visual acuity will be below normal.

All three categories have two outstanding features in common:

First, the patient's binocular function is well developed; the reason for this is that binocular vision (which had already been partially developed prior to the onset of squint) has been maintained because the patient, with the aid of correction where necessary, has always remained binocular for distance.

Secondly, it is rare to get an accommodative convergent squint with a paretic element: therefore these cases are nearly always concomitant. There are, of course, exceptions, the most important being cases which have the so-called A or V syndrome. The A syndrome causes an increase of convergence as the eyes are elevated, although the patient may have binocular single vision on looking down. The V syndrome causes an increase of convergence on depression and there may be binocular single vision on elevation.

Whatever the category of patient, the essential orthoptic tests are the same. The binocular visual acuity for distance and near will be taken with and without correction, on Snellen's and the Near test types respectively. The latent deviation for distance in correction and the manifest deviation without correction will be measured with the Maddox rod and prisms. The latent deviation for near will be measured on the Maddox Wing or on the Klein phorometer. The patient's reactions to the Worth 4-light test and the cover test for distance and near will be recorded. His ocular movement will be investigated.

Finally, the major amblyoscope will be used to ascertain the angle of deviation with and without correction, the strength of the binocular function, the amount of suppression and the fusion range.

As a result of these tests and with the aid, in some cases, of pilocarpine, patients can be divided into those who will and those who are unlikely to require operation. Patients requiring operation are given only two or three pre-operative treatments, mainly with a view to preparing them for their post-operative treatment. Those requiring operation include all adults, most children over 12 whose binocular visual acuity in correction is not up to standard, and teenagers whose correction is low and who wish to leave off their glasses for social occasions. Operation is also required where there is a paretic element. Some children require a short course of up to six orthoptic treatments in order to decide whether operation is necessary. If this short course does not produce any improvement or if the time factor is of importance these children are treated as operation cases.

The post-operative treatment of these patients is extremely important and follows the same lines as the final treatment given to the other group of patients whom it is hoped to cure without operation.

The initial progress of patients in this latter group is, in the first instance, extremely rapid and often spectacular. But a complete and permanent cure requires time and patience and, above all, the co-operation of the child and his parents.

The first objective is to teach the child at the earliest possible stage to realize when his eye is straight and when it is squinting; with patience, this can be achieved even with a child as young as 3 years of age. The second and equally important objective is to stop the habit of squinting by getting the child binocular at all distances in his glasses and to control his squint without glasses. If this can be achieved, the further stages in which the correction is gradually reduced and possibly eliminated altogether, except for close work, can be left until the child is older.

Basically, children can be placed in three groups for treatment:

*Group* 1.—Children under 2½. There is little one can do orthoptically for children as young as this except to eliminate any amblyopia by occlusion or by putting atropine in the fixing eye. Pilocarpine drops used immediately after occlusion will sometimes put an end to an occasional convergence excess.

*Group* 2.—Children between the ages of 2½ and 4, most of whom do not know their letters but who can take an interest in the detail of pictures. With these children, treatment concentrates on teaching them to overcome the convergence excess in their glasses and to control their squint without their glasses.

*Group* 3.—Children who can read or who at least know their letters. With children in this group, it should be possible to make them binocular for distance and near, first with correction, then in a reduced correction and finally, if the hypermetropia is low, without any correction at all.

In the treatment of accommodative convergent squints, instruments, with exception of the bar-reader, play a relatively minor role. Since most of the patients have a manifest deviation for distance without correction, the first step is to teach the patient to control and straighten his eyes when looking at a distant object without correction by making him relax his accommodation. The next step is to repeat this process on a near object, again without correction. His vision will, of course, be blurred whenever he straightens his eyes but the reason for dispensing with any correction for this exercise is that the contrast between the clear and blurred vision is far more marked without correction and is accordingly easier for the child to understand. As soon as he understands and can feel that his eyes are straight, his treatment is continued in correction.

The next stage depends on whether the patient has a convergence excess, that is to say, a manifest deviation for near in correction, If he has, it means that he has to become monocular in order to see clearly and if he controls his deviation by relaxing his accommodation his vision becomes blurred and out of focus. He must therefore be given help in order to clear the blurred vision. In other words, he must be given aids which will reinforce his own efforts to control his manifest deviation for near and turn it into a latent deviation. These aids may consist of convex clip-on lenses or bifocals (or, for emmetropia, a pair of reading glasses) with or without the use of pilocarpine drops. The latter are particularly valuable. Assuming that the child can read or knows his letters, the first step is to get him binocular on large print and to keep him binocular while gradually reducing the size of the print. When he can read N8 to N10 without squinting, he should use his aids for all close work and not merely during exercise periods. He should then be taught to recognize the presence of physiological diplopia with the aid of a torch, in order to prepare him for the effects of a bar-reader so that the bar-reading or bar-spelling exercises can be started. These must be given daily, but with the co-operation of the parents can readily be done at home.

When the child can bar-spell or bar-read small print (but not before) the strength of the clip-on lenses should be gradually reduced until they can be dispensed with altogether; but if pilocarpine is also being used, the drops must be continued throughout.

If, however, it is not possible to get the child binocular for near with aids after a short period of treatment or, having achieved this, to start to reduce the strength of the aids reasonably soon, the probability is that operation is necessary. But assuming that this stage of treatment is successfully completed, the child will have reached the point where, except for being partially dependent on pilocarpine, he is binocular at all distances in correction and has some degree of control without correction. His further treatment is thereafter similar to that which is given to a patient who has no convergence excess, that is, to a fully accommodative convergent squint.

The object now is to improve the binocular visual acuity for distance and near without correction, by making the child less dependent on his glasses. This is done by reducing the correction by means of concave clip-on lenses for short exercise periods with the bar-reader each day or, for the younger children, with pictures at home and in the clinic. This gradual reduction of the correction for the exercise periods is continued until it is neutralized altogether or, if the correction originally exceeded +4·00 D.sph., until it is partially neutralized. When the child can bar-read or bar-spell N6 and has a binocular visual acuity for distance of 6/6 without correction (or an equivalent standard for the higher hypermetrope), the pilocarpine drops, if in use, should gradually be reduced in quantity or strength and finally discontinued altogether. If the standard of binocular visual acuity is satisfactorily maintained, it should then be possible to start reducing the strength of the child's glasses.

The major amblyoscope plays a small but nevertheless important part in this treatment. Initially, it is used to eliminate suppression and to increase the range of fusion. It is also used to help the child to control his squint by relaxing his accommodation and thus reducing

his convergence. In the latter stages of the treatment, it helps to build up a normal relationship between accommodation and convergence. This, in turn, helps to improve the binocular visual acuity.

It is, however, dangerous to pay too much attention to the measurements of the angle of deviation obtained on the major amblyoscope. In all cases of accommodative squint three angles should be measured; the first is the actual angle of deviation in correction: the second is the actual angle of deviation without correction, when the patient is accommodating: the third is the controlled angle measured without correction when the patient's accommodation is relaxed.

These last two angles, measured without correction, will obviously fluctuate according to the amount of accommodation which the patient is using or the extent to which he is relaxing, as the case may be.

The actual angle of deviation measured in correction is usually fairly static but can nevertheless be misleading. A child may register an angle of deviation in correction of as much as +20 degrees and yet have a full compensation, so that he has normal binocular visual acuity for distance and near with and without correction. On the other hand a small angle of deviation of, say +5 degrees to +10 degrees can mask a convergence excess which may not prove amenable to orthoptic treatment. As there is no way of measuring convergence excess on the major amblyoscope, it is of little assistance in helping to decide whether or not operation will be necessary.

Mention has already been made of the possibility of reducing the strength of the child's glasses. But the fact that he may have obtained a good binocular visual acuity for distance and near with and without correction does not mean that he is in a position to dispense with his glasses altogether. Provided that his correction is low, he can in all probability leave off his glasses for short periods each day, the period being gradually increased. If he becomes ill or gets over-tired his squint may reappear but this reappearance will only be temporary and will tend to occur less often as he gets older. Nevertheless, it is most important that the reduction in his correction should be a gradual process and that he should be kept under periodic observation. In any event he will probably still require to use his glasses for reading and school work.

If a child who is using clip-on lenses and bifocals is making normal progress, it should be possible to reduce the strength of these aids approximately every two months. But bifocals are expensive, particularly if they have to be frequently changed, and children on the whole do not make proper use of them. Similar objections apply to the use of a second pair of glasses for reading only, especially as children have a flair for not wearing the right pair of glasses at the right time. On the other hand, clip-on lenses, although somewhat cumbersome and unattractive, can be quickly and cheaply obtained and can be changed whenever necessary without additional cost. Care must be taken, however, when recommending clip-on lenses or reading glasses to ensure that the strength of the lenses which enables the child to be binocular for near does not prevent him from seeing writing at blackboard distance

Finally a word about the advantages of pilocarpine in the treatment of accommodative convergent squints from the orthoptist's point of view. I have myself used it in 43 cases, all of whom were children under 12. In some of these cases the treatment is not yet complete. In 10 cases, I used pilocarpine in conjunction with orthoptic treatment without success, but the fact that the combination of the drops and the treatment produced a negative result enabled me to recommend operation at an earlier stage than I would otherwise have done.

In 21 patients, the use of pilocarpine and orthoptic treatment together has made it reasonably certain that a cure will be obtained without operation.

2 patients, both young children, were not old enough for orthoptic treatment. After occlusion to overcome their amblyopia, they were given pilocarpine drops and became binocular without operation.

5 patients were kept binocular for more than a year with the aid of pilocarpine and in 2 of these it was possible to reduce their correction. Ultimately, with the additional strain of school work, all 5 required operation but by that time their general health had improved and they had reached an age when they were able to co-operate fully in the post-operative orthoptic treatment.

The remaining 5 patients were post-operative. 2 will probably require further operation but in the meantime their binocular state is being maintained with the aid of pilocarpine. In the other 3, their binocular visual acuity has in each case been brought up to normal.

# Section of Experimental Medicine and Therapeutics

President—J. V. DACIE, M.D., F.R.C.P.

[*December* 10, 1957]

## GASTRIC FUNCTION

## The Rate of Gastric Emptying in Patients with Duodenal Ulcer

By J. N. HUNT, M.D., D.Sc.

*Physiological Laboratory, Guy's Hospital Medical School, London*

THE rate of emptying of a meal from the stomach depends in the main on two variables: the propulsive power of the stomach, and the effectiveness of the inhibitory mechanisms which normally check the emptying of the stomach. The receptors whose activity slows gastric emptying lie mainly in the walls of the duodenum and upper part of the small intestine where they are exposed to stimulation by the material leaving the stomach. For example, when the gastric effluent has a high osmotic pressure or when it contains fat, gastric emptying is slowed (Shay, 1944). Once it is appreciated that the rate of emptying depends on a balance between the action of the gastric propulsive mechanism and the action of the inhibitory mechanism in the duodenum, comparisons of the gastric emptying of different individuals can be framed in terms of two questions:

(1) How powerful is the gastroduodenal pump when it is not inhibited?

(2) How effective is the inhibitory mechanism of the duodenal brake?

Thus, for example, rapid gastric emptying might occur either with a very powerful stomach opposed by a normal duodenal brake or with a normally powerful stomach opposed by a very weak brake.

Taking this as our background we have first to find experimental conditions which eliminate as far as possible the action of the duodenal brake.

It has been found that solutions containing 100 mEq. of sodium chloride or of sodium bicarbonate per litre empty about twice as quickly as distilled water (Hunt, 1956). As no other solutions so far tried emptied more rapidly than these, they have been assumed to activate the duodenal brake to a minimal degree. The rate at which these solutions empty therefore reflects mainly the propulsive power of the stomach.

On the other hand, solutions of glucose empty from the stomach more slowly than distilled water because the glucose osmotically activates the duodenal brake. Thus the rate of emptying of strong solutions of glucose depends upon the propulsive power of the stomach, as assessed with solutions of sodium chloride, and upon the effectiveness of the duodenal brake.

It was found that the volumes of the gastric contents in 27 healthy students and 16 patients with duodenal ulcer ten minutes after test meals of 750 ml. of saline were very much the same (Hunt, 1957*a*). If our interpretation is legitimate this result implies that the gastric propulsive power in patients with duodenal ulcer is not different from that in healthy students. It was also found that the stomach emptied meals containing 100 grams glucose/litre at much the same rate in these two groups. From the results it may be inferred that the activity of the gastroduodenal pump and of the duodenal brake which responds to glucose solutions is essentially normal in patients with duodenal ulcer.

The duodenal brake can also be activated by acid in the gastric effluent and it has been found by Shay (1944) that acid is more effective in slowing gastric emptying in patients with anacidity than it is in those with hypersecretion. This finding has been confirmed in normal subjects (Hunt, 1957*b*). The greater the secretion of acid in response to the meal the less is the slowing of emptying produced by adding small amounts of acid to the test meal. Since patients with duodenal ulcer under these conditions secrete on an average twice as much as normal persons one might expect that the slowing of emptying produced by adding acid to the test meal would be less in the patients than it is in the healthy students, but this did not turn out to be so. Thus we may conclude that in these patients the duodenal brake which responds to acid is slightly more reactive than it is in healthy students.

### REFERENCES

HUNT, J. N. (1956) *J. Physiol.*, **132**, 267.

—— (1957*a*) *Lancet*, i, 132.

—— (1957*b*) *Brit. med. J.*, i, 681.

SHAY, H. (1944) *Bull. N.Y. Acad. Med.*, **20**, 264.

# I. Observations on the Cardiac and Pyloric Sphincters in Man

By M. Atkinson, M.D., M.R.C.P., D. A. W. Edwards, M.D., M.R.C.P., A. J. Honour, and E. N. Rowlands, M.D., F.R.C.P.

*Department of Clinical Research, University College Hospital Medical School; and the Department of Gastroenterology, Central Middlesex Hospital, London*

Despite the absence of an anatomical sphincter at the cardia, it has long been suspected that the œsophagus is normally closed off from the stomach by a tonically contracted sphincter which relaxes when food is swallowed. In contrast, despite an obvious anatomical sphincter, there has been some divergence of opinion as to whether the stomach is normally closed off from the duodenum by tonic contraction of the pyloric sphincter, or whether the pylorus is open most of the time. This apparent discrepancy between structure and function at the cardia and pylorus cannot be resolved by radiological methods alone, but manometric techniques should provide conclusive evidence for or against the presence of a sphincteric mechanism. We therefore measured the intraluminal pressure in the cardia from fundus to œsophagus, and in the pylorus from duodenum to antrum, using fine, open-ended, air-filled polyethylene tubes connected to optical manometers recording on photographic paper. The tubes were withdrawn in steps of 1 cm. through the cardia or through the pylorus, and the pressure was recorded at each step (Atkinson *et al.*, 1957, *Lancet*, ii, 918).

*Œsophago-gastric junction.*—When a tube is withdrawn from the stomach into the œsophagus, the position of the recording tip in relation to the diaphragm can be determined by the direction of the inspiratory swing. At about 1 cm. below the diaphragm, the pressure rises above the general level of pressure in the fundus of the stomach and remains higher over a distance of about 2 cm. above the diaphragm, and then falls to the general intra-œsophageal level. This segment of higher pressure, which is interposed between the fundus and the œsophagus, is presumably due to the tonic contraction of circular muscle fibres, since, during the act of swallowing, the pressure in this segment falls to about the general intra-œsophageal level several seconds before the peristaltic wave reaches the cardia. Our observations are in close agreement with those of Fyke *et al.* (1956, *Gastroenterologia*, 86, 135). A mechanism of this kind could not be explained by a valve, but strongly suggests the presence of a physiological sphincter which relaxes as an integrated part of the swallowing reflex. We have shown that this sphincter is independent of the diaphragm (*see below*) and therefore is presumably intrinsic, despite the absence of an anatomical sphincter.

*Pylorus.*—In contrast to the cardia, we have never recorded a segment of sustained high pressure when withdrawing tubes in steps of 1 cm. from the second part of the duodenum through the pylorus into the antrum, despite the presence of the anatomical pyloric sphincter. This implies that the lumen of the pylorus is normally open and the sphincter relaxed. This came as a surprise to us, for we had imagined that the antrum was normally closed off from the duodenum by a tonically contracted sphincter which relaxed from time to time to allow gastric contents to pass through. It seemed possible that our technique was at fault because the position of the recording tips of the tubes could not be controlled with the same precision as at the œsophago-gastric junction, nor was it possible to locate the exact site of the pylorus fluoroscopically during the manometric studies. To circumvent these difficulties, we replaced the open-ended recording tips by balloon-covered tips. Four tiny balloons were tied on to two double-channelled polyethylene tubes with the tapering ends of the balloons overlapping so as to form a continuous pressure-sensitive cylinder 5 cm. long and 7 mm. in diameter. The terminal portions of the tubes distal to the balloons were ensheathed in radio-opaque rubber tubing, which formed a stabilising tail 15 cm. long. This chain of balloons was long enough to ensure that some part of it must lie within the pyloric channel as the tube was withdrawn in steps from the duodenum into the stomach, and pressures could be recorded with certainty at all points across the pyloric region without the necessity of localizing the anatomical sphincter.

It is technically much easier to demonstrate the sphincter at the cardia with this chain of balloons than with open-ended tubes, which tend to slip out of the segment of high pressure. Hence if the pylorus was normally closed by tonic contraction of the sphincter, this continuous chain of balloons could not have failed to demonstrate a sustained rise of pressure. But we have not recorded a band of increased pressure either with open tubes or with balloons in 99 observations in 25 normal subjects, either fasting or when food was present in the stomach. We therefore conclude that the bore of the pyloric channel must have been at least 7 mm. in diameter.

This is not to say that the pylorus never closes. On the contrary, we recorded bursts of phasic pressure waves from the pyloric channel in most of our studies when the antrum and duodenal bulb were in a phase of muscular activity. The waves occurred from 1 to 3

times per minute, each lasting 10 to 15 seconds. These waves must have resulted from obliteration of the lumen of the pylorus, partial or complete; but this closure is intermittent and brief, and occurs as part of a contraction which periodically involves the whole pyloric region and antrum. We could not analyse in detail the time-relationships of these contractions, because each pressure wave lasted only a few seconds, and the recording devices could not be placed with sufficient accuracy in the antrum, pylorus and duodenal cap. However, it is reasonable to suppose that contractions of the pylorus are correlated with those of the duodenal bulb in such a way as to prevent reflux into the stomach. Our records indicate that the pyloric canal can contract simultaneously over a length of 3 to 4 cm., in contrast to the peristaltic contractions of the antrum. These systolic contractions of the pylorus would have the effect of squeezing gastric contents either into the duodenum or back into the stomach, depending on the pressure gradient between antrum and bulb, on the viscosity and lumpiness of the contents, and on the diastolic capacity of the pyloric canal. If the latter fails to relax fully, its systolic output will be correspondingly reduced. A mechanism of this kind might explain the delay in gastric emptying seen sometimes in patients with pyloric and juxtapyloric ulcers where there is likely to be considerable local submucous œdema. It might also explain the delay in gastric emptying so often seen in patients with adult hypertrophic pyloric stenosis, and in the only case we have studied there was certainly no evidence of tonic muscular contraction or "spasm" of the pyloric channel.

*Summary.*—Our manometric studies indicate that the œsophagus is closed off from the stomach by tonic contraction of an intrinsic sphincter which relaxes on swallowing. The pylorus, on the other hand, is normally relaxed and open and does not function as a sphincteric mechanism, but probably acts as a combined filter and pump.

## II. Mechanisms of Gastro-œsophageal Reflux in Hiatus Hernia

By M. Atkinson, M.D., M.R.C.P., D. A. W. Edwards, M.D., M.R.C.P., A. J. Honour, and E. N. Rowlands, M.D., F.R.C.P.

*Introduction.*—Gastro-œsophageal reflux frequently complicates the type of hiatus hernia in which the cardia is displaced into the chest, yet in some patients reflux does not occur despite the presence of a large hiatus hernia. We therefore looked for some factor which might be responsible for the development of reflux, in the hope of shedding some light on the factors responsible for maintaining the competence of the normal cardia.

*Eighteen patients studied.*—18 patients with a hiatus hernia in which the cardia was displaced at least several centimetres into the chest were studied; no true para-œsophageal hernias were included. As a consequence, in these patients, the diaphragm could not be concerned in any closing or valvular mechanism at the œsophago-gastric junction. The functional state of the intrinsic sphincter was assessed by the manometric technique already described (*see above*) and the angle of entry of the œsophagus into the stomach was determined from radiographs. Gastro-œsophageal reflux was assumed to occur if the patient complained of pain, discomfort, or a burning sensation, felt high in the epigastrium or behind the sternum, which was brought on or made worse by lying flat, stooping, or bending; and if acid, bitter, or sour-tasting fluid rose into the mouth at any time.

*The hernial sac pressure.*—In all patients the pressure in the herniated portion of the stomach was similar to that in the stomach below the diaphragm, reflecting the general intra-abdominal pressure, so that both were much higher than the general intrathoracic pressure, to which the intra-œsophageal pressure approximates. The normal gradient of pressure across the œsophago-gastric junction, which obviously favours reflux, was therefore present.

*The cardiac sphincter.*—In the majority of patients a zone of raised intra-luminal pressure could be identified at the œsophago-gastric junction, and swallowing resulted in a transient fall in pressure in this zone. The manometric findings were so closely similar to those in the normally situated cardia that there can be no doubt that an intrinsic cardiac sphincter does exist, and that it may retain its function, to some degree, after herniation of the stomach into the chest.

The height of the elevation of pressure in the sphincteric zone above that in the herniated portion of the stomach has been assumed to be an estimate of the tone of the cardiac sphincter. In a minority of patients no rise in pressure at all was found at the œsophago-gastric junction, that is, the value for sphincteric tone was zero. Normal values were obtained in some patients, low values in others. The presence or absence of symptoms of reflux could be correlated with the tone of the sphincter measured in this way; those patients without symptoms had a high tone in the sphincter, whereas all but one of those with symptoms of reflux had little or no sphincteric tone. The functional state of the cardiac sphincter therefore appeared to be important in the prevention of reflux in hiatus hernia.

*The œsophago-gastric angle.*—The angle at which the œsophagus joined the stomach was assessed to determine whether an acute angle of entry was important in the prevention of reflux. This angle varies to some extent with the position of the patient and the degree of distension of the sac, and in our patients it appeared acute more often with the larger than with the smaller herniæ. On an arbitrary basis the angle was classified as acute or non-acute. The incidence of reflux was approximately equal in these two groups indicating that when the œsophago-gastric junction is displaced into the chest the angle of entry of the œsophagus into the stomach is of little importance in maintaining the competence of the cardia.

*Summary.*—In the presence of hiatus hernia the diaphragm can make no contribution to closure of the œsophago-gastric junction, and the angle of entry of the œsophagus into the stomach plays little part in the prevention of reflux. In these circumstances the cardiac sphincter appears to provide the main barrier to reflux and the competence of the cardia appears to be related to the tone of the sphincter. Why the tone of the sphincter should so often be low in association with hiatus hernia remains to be explained. It is possible that loss of sphincteric tone results from œsophagitis; but it seems more probable that the converse occurs, and that failure of the cardiac sphincter leads to reflux œsophagitis, since the peristaltic function of the musculature of the lowest part of the œsophagus, adjacent to the cardia, was unimpaired in the majority of the patients.

## The Gastric Mucosa in Hypochromic Anæmia

By N. F. Coghill, M.A., M.B., M.R.C.P.
*West Middlesex Hospital, Isleworth*
and A. Wynn Williams, M.D., D.C.P.Lond.
*Dept. of Pathology, Edinburgh University*

Using a modified Wood (Wood *et al.*, 1949) biopsy tube (Coghill and Wynn Williams, 1955), we investigated the gastric mucosa in 84 cases of "simple" hypochromic anæmia, 24 cases of hypochromic anæmia associated with chronic intestinal disorders and 21 patients in whom hypochromic anæmia was found after previous gastric operations, a total of 129.

In the first group, gastritis (Wynn Williams *et al.*, 1957) was found in 38%, superficial gastritis in 8% and atrophic gastritis in 30%. These results were compared with those of Davidson and Markson (1955) and Badenoch *et al.* (1957) who both found a higher incidence, in part explained by differences in their definitions of gastritis.

The incidence of severe gastritis in our cases was twice as high as that in our series of patients with non-ulcer dyspepsia (Wynn Williams *et al.*, 1957).

When the patients were divided into ten-year age groups there was found to be a level incidence of gastritis of about 30% in all groups up to the age of 60 after which it doubled.

Achlorhydria was much commoner among patients with severe gastritis than among those with a normal or near normal mucosa.

Judged by the recommendations of the B.M.A. Nutrition Committee (1950) dietary iron was deficient in 81% of the patients, seriously so in 45%. In 60% there was a history of excessive iron loss through bleeding and child-bearing, considerable in 34%. In 50% there was combined dietary deficiency and loss of iron. There was evidence, not conclusive, of a negative correlation between iron loss and incidence of gastritis. Gastritis was much commoner, relative to iron loss, in the first and last age groups than in the middle groups.

Gastritis may be less frequent in those with a good reason for their anæmia than in those without. Thus gastritis was found in only 12% of the group of patients with chronic intestinal diseases. In 21 patients with hypochromic anæmia after gastric operations severe gastritis occurred in 52%. It was present in 44% of 16 non-anæmic patients with similar operations. These figures are not statistically significant but may represent a trend. Our results do not offer much support for the suggestion that gastritis is a result of chronic iron deficiency (Witts, 1956). On the other hand, there is no convincing evidence yet that gastritis is concerned in the causation of hypochromic anæmia.

### REFERENCES

Badenoch, J., Evans, J. R., and Richards, W. C. D. (1957) *Brit. J. Haematol.*, 3, 175.
British Medical Association, Report of the Committee on Nutrition. (1950) London, B.M.A.
Coghill, N. F., and Wynn Williams, A. (1955) *Brit. med. J.*, ii, 1111.
Davidson, W. M. B., and Markson, J. L. (1955) *Lancet*, ii, 639.
Witts, L. J. (1956) Anæmia and the alimentary tract: The relationship between changes in the alimentary tract and deficiencies of iron, folic acid and vitamin $B_{12}$. The Sydney Watson Smith Lecture, 1955. Edinburgh. The Royal College of Physicians.
Wood, I. J., Doig, R. K., Motteram, R., and Hughes, A. (1949) *Lancet*, i, 18.
Wynn Williams, A., Edwards, F., Lewis, T. H. C., and Coghill, N. F. (1957) *Brit. med J.*, i, 372

## BOOK REVIEWS

**The Essentials of Pædiatrics for Nurses.** By I. Kessel, M.B., B.Ch., M.R.C.P.Lond., M.R.C.P.Edin., D.C.H.Eng. (Pp. xii+213; illustrated. 21s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

The author of this book states in the preface that it deals with the basic principles of this important branch of medicine—pædiatrics, and does not attempt to discuss nursing procedures in relation to the sick child.

This book is well written and well illustrated, but must be read as a companion manual to the standard textbooks. Over-simplicity of statement forced on the author by the small size of the book will often mislead the student nurse. The opening chapter on the normal child and the premature child is excellent. In the chapter on "Affections of the Newborn" there is a section dealing with conditions directly due to the birth process. The scope of the subject is so wide that the author is only able to give a rapid sketch.

The book ends with a chapter on Common Pædiatric Procedures. Appendices on weights and measures, dosage of drugs including the antibiotics, and methods for calculating drug dosage for children are of great value. Finally, there is a list of questions set at the Final State Examination. The answering of these questions will prove to the student nurse that this book is a stimulating guide and companion to her textbook.

**The Respiratory Muscles and the Mechanics of Breathing.** By E. J. Moran Campbell, M.D., Ph.D., B.Sc.Lond., M.R.C.P.Lond. (Pp. xvi+131; illustrated. 20s.) London: Lloyd-Luke (Medical Books) Ltd. 1958.

This is an authoritative work which should be of considerable interest to anatomists, physiologists and, indeed, to clinicians, especially those who have to deal with diseases of the chest. A better knowledge of the muscles of respiration is a necessity in the field of respiratory physiology for they have an effect on respiratory and circulatory functions, as Dr. Campbell has well illustrated by various studies, including electromyographic ones.

The applied aspects of the subject have unfortunately not been included but the author anticipates possible criticisms by noting that there have been few studies in this field about which there is, apparently, much speculation.

The book is very readable, contains a comprehensive bibliography and succeeds in presenting a critical appraisal of previous work.

**The Diagnosis and Treatment of Infections.** By D. Geraint James, M.A., M.D.Cantab., M.R.C.P.Lond. (Pp. viii+234. 30s.) Oxford: Blackwell Scientific Publications. 1957.

This book contains a fund of factual knowledge of advances in specific chemotherapy. Close liaison between the clinician and the laboratory worker is nowadays more important than ever before and the writer attempts with considerable success to bridge the gap between the ward and the laboratory. The book is divided into three parts—part one deals with chemotherapeutic agents, part two with micro-organisms causing human diseases, and part three describes infections as they present in various systems and synthesizes knowledge of the causal agents and their specific chemotherapy, as outlined in the two preceding parts.

One would have liked to see the subject illustrated by well-chosen cases with descriptions, which could give practical illustrations of the attempt at closing the gap between the ward and the laboratory. This would have made the book much more readable.

**An Introduction to Chest Surgery.** By Geoffrey Flavell, F.R.C.S., M.R.C.P. (Pp. 354; 30s.) London: Oxford University Press. 1957.

This is a well-written book, profusely illustrated with uniform negative X-ray illustrations throughout. It covers adequately the field of thoracic surgery, including the lungs, the heart and great vessels, the œsophagus and the diaphragm. The selection of patients for chest surgery is, in the main, well treated and most conditions are illustrated vividly and in a practical manner by well-chosen case histories.

Emphasis is laid on the importance of applied anatomy but it is unfortunate that there is not an equal emphasis on the assessment of pulmonary function, for this is essential in the selection of cases for thoracic surgery.

Some dogmatic statements are made which may not meet with general approval. Moreover the wisdom of undue dogmatism in a book dedicated to students is, perhaps, open to question.

In the preface the author speaks of Trudeau's precept: "Soigner toujours; soulager souvent; guérir quelquefois." Should this not be attributed to Trousseau?

These criticisms apart, the author is to be congratulated on producing a useful, concise and inexpensive work which should have a wide appeal.

**Cerebral Lipidoses.** A Symposium. Chairman: L. van Bogaert. Ed.: J. N. Cumings. Ass. Ed: L. .A. Lowenthal. (Pp. x+212; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1957.

This volume consists of 20 communications on leucodystrophy, cerebral lipidosis and related topics which were presented at a colloquium organized in Antwerp in July 1955 by the Belgian Inter-University Foundation of Neuropathological Research. The majority are followed by critical discussions which reveal very well the problems and controversies of greatest moment in this difficult field of cerebral metabolism. These papers which are well illustrated will prove invaluable to neuropathologists and neurochemists, for many of them are of a histochemical nature and deal with methodology.

Dr. van Bogaert and his colleagues are to be congratulated on having organized this symposium and Dr. J. N. Cumings, the editor, with Dr. A. Lowenthal, associate editor, on having produced a most helpful addition to the rather confused literature on these obscure disorders. It is apparent that symposia followed by the publication of proceedings comprise the most certain way to encourage research in selected fields, and the aim of editors should be to make the wider circle of readers feel that they too have been present at the meeting. On this occasion the editors have succeeded admirably in their duty.

**Zwanglose Abhandlungen aus dem Gebiet der normalen und pathologischen Anatomie.** By Volker Becker, M.D. Heft 1. Sekretionsstudien am Pankreas. (Pp. v+119; illustrated. DM 29.50.) Stuttgart: Georg Thieme Verlag. 1957.

This excellently produced monograph on the pancreas is the first of a series edited by Professors Bargmann and Doerr which will review various aspects of medicine in which the anatomist and pathologist find grounds of common interest. Such integration will be likely to be of benefit to students of both subjects, not least so because it should bring prominently before anatomists the many opportunites that still exist for them to make useful contributions to the furtherance of medicine.

The first half of the book is mainly devoted to the cytology of the acinar cells and the changes that they undergo during the various phases of secretion. It also contains a substantial account of the author's own experimental studies on the cytological effects of certain secretory stimuli, the effect on the exocrine cells of ligations of the main ducts and the results of intoxicating the animal with ethionine.

The second half is primarily a morbid anatomical study in which the author describes his own findings upon several hundred glands, a large number of which were removed before sensible post-mortem changes had developed. In a final section, he has dealt with the effects of obstructions of the main ducts and the lesions found in acute and chronic pancreatitis.

This small monograph with its considerable bibliography should prove useful to anyone interested in the cytology and pathology of the pancreas.

**Medical Jurisprudence and Toxicology.** By John Glaister, J.P., D.Sc., M.D., F.R.S.E., F.R.F.P.S.Glasg. 10th ed. (Pp. xi+720; illustrated. 47s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

This book needs no introduction for it has been long recognized as the most complete textbook on the subject. This new edition has achieved the almost impossible task of including all the relevant dogma of the subject into 720 pages including an index of 25 pages. Not only does it do this but it finds space to devote to such mundane but vital matters as useful weights and measurements, and weights and data of organs including those of the newborn child, of inestimable advantage to those who do not carry such details from memory. At the same time, many new matters have been introduced, such as the anti-human globulin test for human blood and the phosphatase test for seminal fluid, which show the presumptive tests in their true perspective. In respect to the recent changes in the criminal law of England, the authors have endeavoured to cover all relevant points but at the same time they are faced with Scottish Law and this presents such a gargantuan task that it is hardly surprising that minor errors have crept in. In the same manner, the attempt to accede to popular demand to include toxicology in the same volume has produced a dilemma; for to cover even elementary chemical tests on the one hand and the clinical picture upon the other, is impossible in the space available. Even a deliberate omission to describe the more elaborate chemical tests does not solve the problem; for it is with such tests that the future of toxicology lies, such as the ultra-violet and infra-red spectrograph, the X-ray apparatus and the paper chromatograph; whilst such tests as are

enumerated are a possible incentive for those without proper chemical training to indulge in them. It might be suggested without undue criticism that more detail of the symptoms and signs of such matters as poisoning by the organic phosphates would be of greater value.

**An Introduction to Experimental Surgical Studies.** By W. J. Dempster, F.R.C.S. (Pp. 463; illustrated. 50s.) Oxford: Blackwell Scientific Publications. 1957.

This book is intended "for the post-graduate surgical student engaging in experimental surgery". The author feels that the time has now arrived for experimental surgery in the animal laboratory to be recognized as a separate discipline, and that posts for full-time experimental surgeons need to be created. His definition of experimental surgery is important. "Experimental surgery is the systematic investigation of a surgical problem by comparative anatomical and physiological means."

The book does not aim to be a technical manual. "The surgical experimentalist is seeking principles."

The critical commentaries are not all entirely satisfying, but in view of the wide range of subjects discussed this could hardly be otherwise. This work constitutes an original approach to a subject the exact position of which in surgery is often difficult to decide, but which should almost certainly be a more important one than it now occupies in this country. The work is a tribute to the energy and enthusiasm of the author, and should stimulate the further development of experimental surgery along the right lines.

**Cerebral Palsy in Childhood.** By Grace E. Woods, M.D., D.P.H., D.C.B. (Pp. xi+158; illustrated. 27s. 6d.) Bristol: John Wright & Sons Ltd. 1957.

The justification for this monograph on cerebral palsy is its content, comprising a study and analysis of the clinical material collected at Bristol during the last five years, although some of the children have been under observation for fourteen years. Its purpose is to report the method of assessment and clinical evaluation of the condition and to discuss the possible ætiological factors. As in all current work on cerebral palsy the total assessment of the child is emphasized. In all, the study comprised 301 children, less than half of whom were the outcome of a normal pregnancy and delivery.

This book provides rich factual material of particular interest and use to those working on the condition, for it supplies information for comparative work. The discussion occupies a minor part, which, in a subject so incomplete as cerebral palsy is to be regretted. The reader hoping to find speculation or new ideas for fresh lines of thought arising from such a wealth of clinical observation and examination will be disappointed.

**The Clinical Application of Hormone Assay.** By John A. Loraine, M.B., Ph.D.Ed., M.R.C.P.Ed. (Pp. xii+368; illustrated. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

This book sets out to review methods of hormone assay and the results of their application so far to clinical problems, and to indicate directions in which they may profitably be employed in the future. It is a wholly admirable publication. A wealth of information is matched by the simplicity of its presentation. It will satisfy all who wish to acquire some understanding of this increasingly important subject, as well as serious workers in the endocrine field.

The work starts with a chapter on general principles. There follow chapters on the steroid hormones including œstrogens, progestogens, corticosteroids and androgens, with final chapters on the catechol amines and insulin. A simple but thorough account is given of the chemistry of each group of hormones; the reviewer found this particularly helpful in the case of the steroids. The various methods of assay available for each group of hormones are explained simply, and their relative values critically reviewed. The reviewer perused it with delight and immense profit. The book is a model of its kind and is highly recommended.

**Portal Hypertension.** By Alan Henderson Hunt, M.A., D.M., M.Ch., F.R.C.S. (Pp. xi+230; illustrated. 40s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

This is one of the two Jacksonian Essays for 1956 whose authors were awarded prizes. It comprises a clinical study of 250 cases of disease which may affect the portal venous system and cause portal hypertension. The majority of cases are, as would be expected, due to cirrhosis of the liver, but a few extraneous conditions such as compression or invasion of the portal vein by tumour are included.

Chapters on the anatomy and pathology are followed by others on the effects and clinical manifestations of portal venous obstruction and the operative treatment. The author describes the method which he and Professor Mayneord devised to measure the speed of flow in the portal vein using radioactive sodium. Appendices deal with technical details and about a hundred selected case histories.

Publication as a book in the form in which the essay was submitted has some disadvantages, particularly in that the case histories, being all placed at the end, are not so easily accessible as illustrations of particular points, and some of them might well have been omitted. There is a comprehensive list of references.

This is an excellent account of a well-documented clinical study. It does not set out to be a guide. It should, however, be read by all who have to treat these cases for it shows what has been done by a surgeon who has given much skill and careful thought to the problems. The book is profusely illustrated, and the X-ray reproductions are particularly good.

**Essentials of Chemical Pathology.** By D. N. Baron, M.D. (Pp. xii+247; illustrated. 25s.) London: English Universities Press. 1957.

Dr. Baron has succeeded in presenting his subject succinctly and has given the reader—medical student or registrar—an adequate appreciation of the chemical pathologist's work in relation to the patient and his disease. The underlying principles of the methods suggested are emphasized rather than their details and considerable attention is devoted to the interpretation and significance of the actual findings. The knowledge of such principles is invaluable and will make collaboration with chemical pathologists more real and useful than it sometimes may be. The first five chapters cover general chemical pathology, namely water electrolyte, carbohydrate, protein and lipid metabolism and the last six chapters discuss the chemical pathology of the endocrine glands, bone, liver, kidneys, alimentary canal, and the cerebrospinal fluid. The chemical pathology of the steroid hormones and the various plasma proteins is given in some detail but iron metabolism and hæmoglobin have been excluded. No claim is made that the book is a reference text. There is, however, a useful list of books for further study if desired and also a useful list of normal values both in the adult and the child. The book requires careful reading, it presents the essentials with no padding but it fulfils satisfactorily the purpose for which it was intended, namely to act as a guide in the rapidly growing study of chemical pathology.

**Uses of Epidemiology.** By J. N. Morris, M.A., F.R.C.P., D.P.H. (Pp. viii+135; illustrated. 17s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

The value of epidemiological methods in the search for causes of non-communicable disease is now becoming widely recognized. The same methods may also be used by public health workers for examining trends in disease, in taking stock of the health of a community and its way of life, and for evaluating health services in relation to constantly changing needs. The uses of epidemiology are less well recognized by the clinician though it may enable him to define syndromes and to understand the full breadth of a disease from its earliest and often inapparent stages to death. Finally estimates of prognosis for the individual can only be made from knowledge of the general experience and the factors which influence it. These are the subjects with which this small book is concerned. Though it contains much factual information on many diseases and though most epidemiological methods and principles are referred to, it is not intended as a textbook, being neither comprehensive nor sufficiently systematic. Infectious diseases and those with a microbiological component are deliberately omitted. Though justifiable this is perhaps a defect in a book that appears to aim at bringing together the contributions of clinical medicine, laboratory work and public health in the common discipline of epidemiology.

It is a lively and stimulating book, well illustrated by tables and graphs. It is so admirably brief that inevitably there are some controversial and challenging statements for which little evidence is given. This is hardly a criticism if the reader is thereby provoked to inquire further, and more than 200 excellent references are provided to help him on his way.

There has long been the need for a book which explains the potentialities of the epidemiological approach to those engaged in clinical medicine in terms that they appreciate. It should prove of particular value to medical students and will also be useful to students and workers in public health.

**Operative Surgery.** Editors: Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. In 8 volumes and index. (Volume 6 Hand, Amputations, Plastic Surgery, Gynæcology and Obstetrics; illustrated. £5 10s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

This volume follows successfully the same methods of illustrative description used in the volumes previously reviewed. A fairly intensive testing of the index revealed no errors. The system of separate numbering of the different sections of each volume, however, makes the tracing of a reference a little more difficult than with volume numbering, and would not seem to have any special advantages.

*Proceedings of the Royal Society of Medicine*

Vol. 51
469

# Section of Laryngology

President—R. J. CANN, M.S., F.R.C.S.

[*February* 7, 1958]

## DISCUSSION ON VIRUS INFECTIONS OF THE UPPER RESPIRATORY TRACT

**Dr. C. H. Andrewes** (London):

Virus infections of the upper respiratory tract cover the most important causes of disability and absenteeism in the working population. The problem they pose is unsolved largely because they represent a heterogeneous collection of illnesses, and I shall discuss their ætiology. Influenza may present itself occasionally as a very mild disease with coryza, and acute tracheo-laryngitis may be due to influenza, to the common cold, to adenoviruses or, most commonly of all, to agents yet undiscovered. The responses of the respiratory tract to viruses are limited in variety; so it is hardly surprising that the clinical pictures of these various infections overlap widely. During an epidemic due to one of them, a pattern can be discerned, but the sporadic case is apt to baffle the wisest clinician.

We may, of course, be asked whether it matters which virus is causing a particular case of tracheitis. We do not know that it affects either prognosis or, in the present negative state of virus chemotherapy, treatment. The importance is, I feel, a long-term affair. We have to disentangle this skein before we can hope to understand the epidemiology of these things, or hope to control them through vaccination or any other means.

Several techniques, or a combination of them, have been found useful for cultivating and identifying respiratory viruses. First, the influenza viruses, and some others, can be grown in fertile developing hens' eggs by various techniques. Most generally, they are isolated after inoculating into the amniotic cavity but can soon be adapted to growth in the more convenient allantoic cavity (Table I).

TABLE I

| | | Growth in | | | |
|---|---|---|---|---|---|
| | | Embryonic tissues of egg | | Tissue culture | |
| | Growth detected by → | Hæmagglutination | Infection of animals | Cytopathic effect | Hæmagglutination |
| Myxoviruses | Flu A | + | + | + | + |
| | Flu B | + | + | + | + |
| | Flu C | + | − | − | − |
| | Sendai | + | + | ? | ? |
| | C.A. | + | − | + | + |
| | Adenoviruses | − | − | + | − |
| | Chimpanzee viruses | − | − | + | − |
| | 2060 and JH | − | − | + | − |
| | Common cold | − | − | ?± | ?± |

Second, embryonic fluids so infected will agglutinate red cells of fowls and various mammals, and the viruses can thus be readily titrated.

Third, some of the viruses will grow *in vitro* in tissue cultures of human, monkey or other species. Their presence can be recognized by destructive—cytopathogenic—effects on the cultures, or by the production of a hæmagglutinin, as in the chick embryos.

Fourth, it is possible to test for multiplication of virus in chick embryo or in tissue culture by inoculating material into animals, to see if disease is produced: this includes putting material into the human nose, to see whether colds result.

Finally, wherever a positive result is obtained, an attempt can be made to neutralize it with specific antisera; or diagnosis can be established by use of the complement-fixation test. Usually it is necessary when using any of these tests for diagnostic purposes to compare "acute" and "convalescent" sera to look for an antibody rise, since many "normal" human sera contain some antibody to these various viruses. I can now list at least 9 upper-respiratory viruses and the tests which are applicable to their diagnosis.

*Influenza A* is easily isolated in eggs or in tissue culture from nasal washings or gargling taken early in the disease. It hæmagglutinates, and specific sera readily show what it is. But there is one complication—it changes its antigenic make-up from one epidemic to another, sometimes very radically, as happened in 1957. The hæmagglutinin-inhibition test then fails to reveal its true nature. However, by complement fixation all influenza A strains are alike, so we should not be led astray. If virus is not isolated, a diagnosis can still be made by examining paired sera and detecting a rise in hæmagglutinin-inhibiting or complement-fixing (c.f.) antibodies. Since normal human sera rarely contain much c.f. antibody, a good titre in a single, convalescent specimen, is presumptive evidence of infection.

*Influenza B* behaves very similarly: it rarely causes such widespread epidemics as does A, and its changes in antigenic make-up seem to proceed more slowly. Normally the presence of virus is detected in embryonic fluids by hæmagglutination, but it is possible to do so by producing fever and rhinitis in ferrets, or pneumonia in mice.

*Influenza C* is probably an uncommon cause of clinical infection in man. It has been reported in association with actual outbreaks, sometimes alongside influenza A. Antibodies against it may be widespread, but subclinical infection is probably common.

*Sendai virus or hæmagglutinating virus of Japan.*—This has also been called influenza D, but the biological properties of the virus are nearer those of mumps than of influenza A. It was first described as causing pneumonitis of newborn children in Japan; also as being present as a latent infection of laboratory mice, both in China and Japan; and as causing epidemics amongst pigs. A human epidemic due to the virus has been reported from Vladivostock, but I have seen no details. Presence of antibodies in human sera is reported from Britain and the U.S.A. but their significance is obscure, especially as virus has not been isolated outside Asia. There seems at present no good reason to use the term influenza D.

The *CA* (*croup-associated*) virus described by Chanock and by Beale may belong with the preceding hæmagglutinating viruses which are classified as myxoviruses. It was isolated in tissue cultures but also grows in eggs. Its importance as a cause of human disease is unknown, but serological evidence indicates that it is widespread, whether causing clinical or subclinical infection.

*The adenoviruses.*—These viruses are recognized by ability to grow and produce destructive effects in tissue cultures of various kinds. By neutralization tests in tissue cultures they can be divided into numerous serological types but they possess a complement-fixing antigen in common. They were first recognized as causing latent infections of human tonsils and adenoids but turned up, soon after, as causes of acute respiratory infections, especially among recruits. Conjunctivitis sometimes goes along with acute pharyngitis and the term pharyngo-conjunctival fever has been used. The infection probably corresponds in large part to the febrile catarrh which Stuart-Harris, Wilson Smith and I wrote of in 1937 as affecting service units. Types 3, 4 and 7 seem chiefly concerned in these outbreaks; though they occur in civilian life, their importance outside the Services is still undetermined. Most studies indicate that cases of febrile catarrh amongst civilians are largely caused by agents yet unidentified. Adenoviruses also cause one form of primary atypical pneumonia.

*Chimpanzee viruses.*—Two groups of workers in America have described two different viruses causing "common colds" in chimpanzees and possibly associated also with colds in man. There is again serological evidence that at least one of these is widespread as a human infection.

2060 *and JH viruses.*—Again we have two groups of workers in America who have isolated viruses, this time very similar ones, associated with colds or something like colds. These grow in tissue cultures of monkey kidney. Winston Price's JH virus recently attracted considerable attention in the American press, when he described attempts at protective inoculation of children; this was hailed as a common cold cure. There is, in fact, little reason to believe that the JH virus is a major cause of colds. In our hands at the Salisbury Common Cold Research unit, cultures of JH virus have not produced colds on instillation into people's noses. The virus does, however, frequently persist for some days in the nose and it is possible, though not yet certain, that cultures may cause colds after one or more human passages.

*Common cold.*—Several viruses already mentioned might be considered as candidates for causes of common cold. There are 3 others, 1 from our laboratories at Salisbury, 2 from abroad, which might also have claims; these claims we are investigating. There is also the "cold" virus which we cultivated in 1953 and then lost. Findings such as these now coming to light are making me wonder "Is there *a* common cold virus? or have we

deal with a hydra?" It will be recalled that Hercules had some trouble in destroying this animal, for every time he cut off one of its many heads it sprouted a new one. So we may identify and even learn to immunize against *a* common cold virus, only to find that a new virus has taken its place. We do know that there must be more than one virus giving symptoms commonly diagnosed as colds. We have propagated in series one line which has a regularly longer incubation period than do most others—about four, as against two or three days. Susceptibility to inactivation by ether is a property which differentiates some groups of viruses from others. Our tests against different strains of cold viruses have given different results, suggesting that in this respect also cold viruses may not be uniform.

We are learning almost month by month of new respiratory viruses and how to recognize them. The problem is a difficult one but we now have clues which could lead to its solution.

**Professor C. H. Stuart-Harris (Sheffield):**

The traditional clinical classification of the acute infections of the respiratory tract was based on the anatomical position of the area chiefly involved. Rhinitis or the common cold was thus distinguished from pharyngitis or tonsillitis and these in turn from laryngitis and bronchitis. There existed, however, diseases such as diphtheria, scarlet fever or influenza in which the sum total of clinical characters enabled their recognition as clinical entities and these were readily associated with the causative organisms when the latter were recovered. The correlated clinical and laboratory studies on influenza which were made in this country in 1937 not only confirmed historical views on the clinical pattern of this virus infection but emphasized the difficulty of a differential diagnosis based purely on clinical features. Catarrhal conditions of the respiratory tract characterized by an acute pharyngitis or by a combined pharyngo-laryngo-tracheitis were thus found to be frequently unassociated with the influenza viruses (Stuart-Harris *et al.*, 1938).

The diagnosis of acute viral infections of the upper respiratory tract must start by excluding bacterial infections which in any case provide a minority of the cases commonly encountered. In a recent large series of cases of acute respiratory disease among students at the University of Wisconsin, Evans (1957) found that only 16·3% of 2,331 patients exhibited infections which could be attributed to bacteria. It must be remembered, however, that hæmolytic streptococcus infection, Vincent's angina, and the anginous form of infectious mononucleosis constitute important differential diagnoses of catarrhal pharyngitis in its exudative form which is now recognized as one form of adenovirus infection.

Another important principle is the anatomical and functional unity of the whole respiratory tract. Upper respiratory tract infections by viruses such as influenza or the adenoviruses are frequently accompanied by lower respiratory tract involvement. The epithelium of the respiratory tract furnishes a continuous sheet of cells which is often attacked indiscriminately by influenza virus "browsing over" the mucosa. We know little of the extent of the attack by other viruses such as the common cold virus which cannot be studied readily in the laboratory.

*Syndromes of Acute Respiratory Disease*

(1) *Influenza.*—We come now to the four main syndromes: influenza, the common cold, atypical pneumonia and febrile catarrh with particular reference to the pathological changes seen in the upper segment of the respiratory tract. This can be regarded as the area from nose to larynx with the extension to the conjunctiva, nasal sinuses and middle ear. Influenza virus appears most characteristically to attack the posterior nasopharynx and the mucosa of the nose rather than that covering the tonsils or anterior pillars of the fauces. A dry granularity of the posterior pharyngeal wall without obvious exudate results. The anterior fauces may appear normal though the uvula is sometimes reddened. The throat may or may not be sore on swallowing but this symptom is not prominent. Epistaxis, however, may be severe and often unexpected because coryza may have been inconspicuous though the nose is often blocked. The conjunctivæ are usually involved in influenza so that mild suffusion results and occasionally lacrimation is intense. Cervical gland enlargement is unusual and trivial in degree. It is perhaps important to stress that the individual clinical illness bears no particular relation to the exact causative strain of the influenza virus. Influenza A and B look the same and feel the same to the doctor and patient and chest complications occur in both. The larynx usually comes in for a share of the pathological effects but a husky voice is commoner than one which has obviously lost most of its tone. Occasionally aphonia is present. The emphasis upon general malaise, the aches and pains, the headache and fever all assist in diagnosis. There is almost invariably a cough and sputum is far from infrequent.

Influenza virus infection fortunately clears up with little tendency to attack the sinuses or middle ear though this rule is occasionally broken. I have seen little tendency to subsequent streptococcal disease, and pneumococcal infections have usually been confined to the chest. The *Staphylococcus pyogenes* has been the most important secondary invader in cases of influenza during the recent Asian virus outbreak.

(2) *The common cold.*—The common cold has so far triumphed over the virologist but clinicians cannot claim any better luck in treatment of the patient. Largely an afebrile disease with transient constitutional involvement, the cold is unfortunately a great source of trouble in both upper and lower respiratory tract. The profuse watery discharge is usually unaccompanied by much pharyngitis or laryngitis. In those prone to chronic disease of the chest, however, rhinitis is soon succeeded by a "cold on the chest" with increased cough and sputum. It seems probable that sinusitis and otitis media follow the cold virus in some persons as night follows day so that there is a constitutional or even a mechanical factor which determines the particular clinical picture. Whether or not a particular species of bacteria stalks along with the cold virus is unknown but in the chest the *Hæmophilus influenzæ* and pneumococci cause most trouble; in the throat the increased carriage of pneumococci has been noted by many workers and perhaps this may be related to the occurrence of sinusitis or otitis media.

(3) *Atypical pneumonia.*—Until more is known of the ætiology of the common cold, it will be impossible to say whether certain sequelæ of the cold such as aspiration pneumonia are, as some authors maintain, due to mechanical factors created by mucus or whether they are essentially infective episodes. Clinically, however, it is hard to distinguish an aspiration pneumonia occurring after an upper respiratory infection from an atypical pneumonia in which the nose and throat are also involved. None of the agents belonging to the psittacosis group or *Rickettsia burneti* which can cause atypical pneumonia can be regarded as being particularly pathogenic for the upper respiratory tract. Eaton's virus of atypical pneumonia (Eaton, Meiklejohn and van Herick, 1944) has been shown to cause atypical pneumonia associated with an increased titre of red cell agglutinins in the serum active at refrigerator temperatures. This virus grows particularly well in the bronchial epithelium of the chick embryo (Liu *et al.*, 1956; Liu, 1957). Perhaps in man it exhibits a wider predilection for ciliated columnar epithelium and thus causes rhinitis, pharyngitis or tracheitis, but much more work is needed upon the relationship of this agent to human respiratory disease.

(4) *Febrile catarrh and adenoviruses.*—The condition of the respiratory tract classified by us as "febrile catarrh" and by American workers as acute respiratory disease (A.R.D.) probably includes several different virus infections. In 1938 the existence of acute pharyngitis or tonsillitis in servicemen suffering from an influenza-like disease was established as a point of contrast from influenza A. Usually there was general injection of the fauces so that the tonsils and uvula as well as the pharynx appeared bright red. Occasionally petechial hæmorrhages were present on the soft palate. Some patients developed an exudate on the tonsils which was hard to distinguish from streptococcal tonsillitis. At times follicular, the exudate was sometimes more diffuse and glairy or even frankly mucopurulent and yet hæmolytic streptococci were absent. The throat was usually very sore, the voice often hoarse and the trachea was often involved as shown by a painful, irritating, barking cough. Cervical lymph gland enlargement occurred in half the patients who were studied but was not usually considerable in degree. Yet this exudative pharyngitis, as it was termed by the U.S. Commission on acute respiratory diseases during the war (Commission on A.R.D., 1944, 1947), was inconstant. Other patients with A.R.D. had little or no physical signs and resembled those with influenza. Still others exhibited a profuse catarrh from the nose resembling a heavy cold.

Both in the U.S.A., where adenoviruses were first recovered, and in Britain, the syndrome of febrile catarrh in servicemen has been shown to be related to certain types of virus chiefly Types 4 and 7. In some American service establishments 60% of the cases of acute respiratory disease have been due to the adenoviruses (Hilleman *et al.*, 1955). Yet in Britain, the adenoviruses, though causing outbreaks in 1955 (Andrews *et al.*, 1956; Tyrrell, Balducci and Zaiman, 1956) have been relatively infrequent as a cause of acute illness even in the Forces.

Among the civilian population children appear to bear the brunt of the attack of adenovirus infection. American workers were again early to the fore with their account of conjunctivitis accompanying pharyngitis in children and this caused them to classify outbreaks of the disease as "pharyngo-conjunctival fever" (Bell *et al.*, 1955). Similar outbreaks occurred in Britain and elsewhere in Europe chiefly in 1955. A conjunctivitis has been present, though far from constant, and the rest of the clinical picture has conformed to the febrile catarrh of the soldier. Types 3, 7 and 14 have caused such illnesses in schools-

children in Britain (Kendall *et al.*, 1957). Apart from these outbreaks and others limited to conjunctivitis it has been difficult to attribute much clinical disease to the adenoviruses. Some virologists indeed consider the adenoviruses to be characteristically latent viruses causing a state of chronic infection which persists even though serum antibodies may be present as in the case of herpes virus. The possible role of the adenoviruses as a cause of tonsillar or adenoidal hypertrophy is worth consideration because it is in these glands removed by the surgeon that a high percentage of latent adenovirus infection has been demonstrated. As many as 90% of glands removed surgically harbour adenoviruses chiefly of Types 1, 2 and 5 (Huebner *et al.*, 1957).

Yet strains of adenoviruses such as Types 1 and 2 which have been recovered from adenoids have been shown to be fully pathogenic for the human volunteer both in this country and the U.S.A. The person inoculated with these viruses usually develops an acute febrile respiratory disease often with an anterior pharyngitis (Roden *et al.*, 1956; Bell *et al.*, 1956).

It seems, however, that the adenoviruses cannot be blamed for much of the endemic acute respiratory disease which attacks each winter and produces the familiar acute family outbreaks of illness varying from coryza to acute bronchitis. Huebner, Bell and Rowe (1957) consider that about 5% of febrile illness in the pre-school child is due to the adenoviruses; between 6 and 17 years of age only 2·65% of illnesses are so related, and the frequency for adults is only 0·3%. Even the ordinary acute sore throat of civilian practice which fails to yield the hæmolytic streptococcus does not invariably yield adenoviruses on cultivation of throat swabs (Jordan, 1957). The studies made in Sheffield in 1955 on servicemen and civilians (Tyrrell, Balducci and Zaiman, 1956) showed that much of the problem of febrile catarrh remains after separation of the illnesses for which known viruses can be blamed.

How many of these illnesses may be due to the cold virus or to agents such as the laryngo-tracheo-bronchitis virus of Chanock (1956) or the JH virus of Mogabgab and of Price (Pelon *et al.*, 1957; Price, 1956) is for future workers to decide. The story of much of the acute respiratory disease due to viruses is unwritten.

## REFERENCES


ANDREWS, B. E., MCDONALD, J. C., THORBURN, W. B., and WILSON, J. S. (1956) *Brit. med. J.*, i, 1203.

BELL, J. A., ROWE, W. P., ENGLER, J. I., PARROTT, R. H., and HUEBNER, R. J. (1955) *J. Amer. med. Ass.*, **157**, 1083.

——, WARD, T. G., HUEBNER, R. J., ROWE, W. P., SUSKIND, R. G., and PAFFENBARGER, R. S., Jr. (1956) *Amer. J. publ. Hlth.*, **46**, 1130.

CHANOCK, R. M. (1956) *J. exp. Med.*, **104**, 555.

Commission on Acute Respiratory Diseases (1944) *J. Amer. med. Ass.*, **125**, 1163; (1947) *J. Amer. med. Ass.*, **133**, 588.

EATON, M. D., MEIKLEJOHN, G., and VAN HERICK, W. (1944) *J. exp. Med.*, **79**, 649.

EVANS, A. S. (1957) *New Engl. J. Med.*, **256**, 377.

HILLEMAN, M. R., GAULD, R. L., BUTLER, R. L., STALLONES, R. A., HEDBERG, C. L., WARFIELD, M. S., and ANDERSON, S. A. (1957) *Amer. J. Hyg.*, **66**, 29.

HUEBNER, R. J., BELL, J. A., and ROWE, W. P. (1957) In: ALLFREY, V. G., *et al.*, Cellular Biology, Nucleic Acids and Viruses. New York Academy of Sciences, New York, **5**, 394.

JORDAN, W. S. (1957) *Ann. N.Y. Acad. Sci.*, **67**, 273.

KENDALL, E. J. C., RIDDLE, R. W., TUCK, H. A., RODAN, K. S., ANDREWS, B. E., and MCDONALD, J. C. (1957) *Brit. med. J.*, ii, 131.

LIU, C. (1957) *J. exp. Med.*, **106**, 455.

——, EATON, M. D., and HEYL, J. T. (1956) *Bull. N.Y. Acad. Med.*, **32**, 370.

PELON, W. MOGABGAB, W. J., PHILLIPS, I. A., and PIERCE, W. E. (1957) *Proc. Soc. exp. Biol. N.Y.*, **94**, 262.

PRICE, W. H. (1956) *Proc. nat. Acad. Sci., Wash.*, **42**, 892.

RODEN, A. T., PEREIRA, H. G., and CHAPRONIERE, D. M. (1956) *Lancet*, ii, 592.

STUART-HARRIS, C. H., ANDREWES, C. H., and SMITH, W. (1938) *Spec. Rep. Ser. Med. res. Coun., Lond.*, No. 228.

TYRRELL, D. A. J., BALDUCCI, D., and ZAIMAN, T. E. (1956) *Lancet*, ii, 1326.


**Mr. J. Angell James** asked the opening speakers if they had any particular views on the histological changes and also on the treatment in these virus diseases.

In a small number of cases of the common cold he had taken biopsy specimens from the nasal mucous membrane and cultures from the secretion at different stages. He noted that in the first two days the secretions were usually sterile and the mucous membrane showed a lymphocytic infiltration. After the second day, the secretion usually gave a culture of streptococcus, staphylococcus, pneumococcus or other organisms and the cellular response changed to polymorphonuclear infiltration.

It was now realized that animals and birds may be reservoirs of human diseases more often than has been thought in the past. Recent instances were psittacosis from parrots and acute polyneuritis from cats suffering from enteritis, the latter described by Dr. Malcolm Campbell (1958, *Proc. R. Soc. Med.*, **51**, 157). Was there any evidence that the very common virus pneumonia of swine was connected with human respiratory tract infection?

**Mr. Ronald Macbeth** asked the opening speakers whether the isolated acute injection of the uvula with cherry-like swelling was due to a virus infection? What, if any, was the relation of herpes simplex to colds? Had hot whisky in supposedly adequate dosage any useful effect on the progress of virus infections?

**Mr. S. W. Allinson** asked if the morphology of the viruses which had been mentioned was known. If this were so, what was the relationship between the phase of the virus and the phase of the disease?

**Dr. C. H. Andrewes** (in reply) said that there was no evidence of a relation between virus pneumonia of swine and human infections.

A latent infection with herpes simplex virus might be activated by a common cold infection, as by various other infections.

Electron microscopy could make visible influenza and adenoviruses; there was no obvious relationship between any morphological changes in the virus and the phase of the disease.

**Professor C. H. Stuart-Harris,** in reply to Mr. James, said that so far as the bacteriology of these virus diseases was concerned, it was generally agreed that any of the nasopharyngeal bacteria could cause secondary complications. It was only against these organisms or against the uncommon viruses of the psittacosis group and *Rickettsia burneti* that chemotherapy was at all effective. Chemotherapy against the smaller viruses was not yet applicable and thus there was no specific treatment for any of the common virus diseases of the upper respiratory tract.

In reply to Mr. Macbeth, it was probably wrong to think that particular viruses had a predilection for special anatomical areas of the respiratory tract. A red uvula was common in influenza but it was not confined to this disease. Whisky was the traditional friend of the sufferer from the common cold—it probably made the patient *feel* better.

[*March* 7, 1958]

THE following short papers were read:

**Herpes Zoster of the VII, VIII, IX, X and XI Cranial Nerves.**—Mr. B. S. CARTER.

**Dysphagia Resulting from Tuberculosis of the Axis.**—Mr. KENNETH HARRISON.

**Acute Epiglottitis and Supraglottitis (Acute Supraglottic Œdema).**—Mr. H. MORUS JONES.

**Mucous Membrane Pemphigus.**—Mr. ALAN G. GIBB.

**Two Cases of Wegener's Granulomatosis.**—Mr. CHARLES SMITH (for Mr. W. A. MILL).

**Self-mutilation of the Tongue.**—Mr. J. F. NEIL.

**Leiomyoma of Larynx.**—Mr. B. H. PICKARD (for Mr. W. I. DAGGETT).

The papers were discussed by Mr. MYLES FORMBY, Mr. WILLIAM MCKENZIE, Mr. KENNETH HARRISON, Mr. H. MORUS JONES, Mr. DAVID BAWTREE, Mr. H. V. FORSTER, Mr. C. S. SAVAGE, Mr. E. D. D. DAVIS, Mr. MAXWELL ELLIS, Mrs. F. CAVANAGH, Mr. I. S. YOUNG, Mr. J. F. LIPSCOMB, Professor V. LAMBERT and Mr. T. L. BRADBEER.

The meeting will be reported in the *Journal of Laryngology*.

# Section of Medicine

President—W. A. BOURNE, M.A., M.D., F.R.C.P.

[*February* 25, 1958]

## DISCUSSION ON SKELETAL MANIFESTATIONS OF GENERAL DISEASE

**Dr. Douglas Hubble** (Derby):

Bone is a dynamic, living structure; but only a small part of the adult skeleton—perhaps 10%—is affected by the daily give-and-take, the active accretion-resorption process, which is the evidence of its life. Even in a disease, therefore, such as post-menopausal osteoporosis, in which resorption is outstripping accretion, it will be some years before the clinical appearances are diagnostic. Our methods of examination are still inexact, and it has, for example, been calculated that 60% of the bony matrix of a vertebra must disappear before radiographical evidence of osteoporosis is demonstrable (Babaiantz, 1948).

In children, there is a growing, maturing skeleton under our eyes, and quite small deviations from the average can easily be detected. For example, Hewitt *et al.* (1955) showed, by the radiographical study of Harris lines and epiphyseal development, that trivial illness in children will produce arrest of linear growth, but that skeletal maturation remains unaffected. These two aspects of bone-growth—deposition of the bone matrix, and skeletal maturation—are disturbed in differing degree by different agencies, but I will first discuss Cushing's syndrome, in which both are affected. Albright (1943) stated that in Cushing's syndrome the effect of corticosteroids on protein metabolism was not catabolic but anti-anabolic, and Dr. Sissons will confirm this hypothesis in his analysis of the bone-changes.




A B

FIG. 1 (*Case I*).—Cushing's syndrome: A, before and B, sixteen months after operation; growth of 5 in.

*Case I.*—R. K., a boy aged 8½ years, suffered from Cushing's syndrome, due to adrenocortical hyperplasia. According to his parents, the disease had existed for two to three years when Fig. 1A was taken, and he was stated to have grown only half an inch in the previous two years. Fig. 1B shows him sixteen months after treatment by bilateral adrenalectomy, during which time he grew 5 in., an average height increment for more than two years. In Fig. 2 are shown comparable X-rays of tarsus and carpus, the upper radiograms being taken before, and the lower radiograms fourteen months after, the final operation. The osteoporosis has disappeared and the bone-texture now appears to be normal. The epiphyseal development has advanced at a remarkably rapid rate. I estimate from these and other sites that the bone-age, which was originally between 5 and 6 years on the 50 percentile, advanced between four and five years in the year after operation.

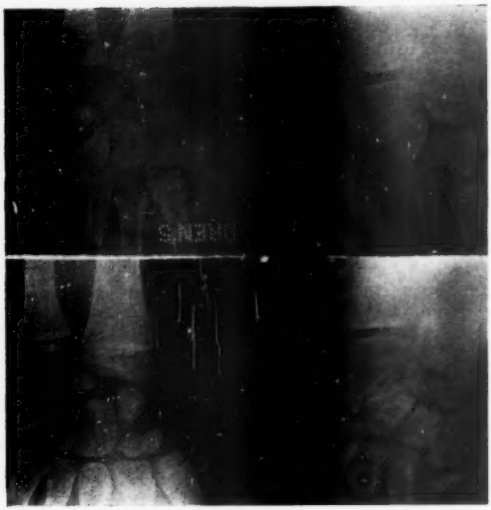


FIG. 2 (*Case I*).—Correction of osteoporosis and advance of skeletal maturation by four to five years during fourteen months after operation.

I have seen such rapid skeletal maturation only in the treated—indeed, in the over-treated—cretin, and I assume that it must have been due to the release of the growth and thyroid hormones from the depressive effect of corticosteroids. Corticotrophin has been shown to be directly antagonistic to growth hormone in the rat, and thyroid depression has frequently been suggested as occurring in Cushing's syndrome.

*Corticosteroid Therapy*

The effects of long-continued corticosteroid therapy on bone structure require careful observation, particularly so in post-menopausal women in whom there is already a disposition to osteoporosis; in the treatment of diseases such as rheumatoid arthritis where osteoporosis is already part of the disease process; and in children in whom the needs for growth are paramount. An ill effect on the skeleton is easily assessed in children by serial height-measurements; and in women the Sulkovitch test provides an easy index of osteoporosis. The reports in the literature of vertebral fracture occurring during corticosteroid therapy are numerous. High protein diets and the use of a protein-anabolizer, such as methyl testosterone, or the new drug 17-α-ethyl-19-nortestosterone, are rational and effective therapies.

*Osteoporosis*

Osteoporosis is a state in which the accretion of the protein matrix of bone has not kept pace with normal resorption, or in which abnormal resorption is outstripping accretion. The osteoblast is the agent of accretion, and the osteoclast is responsible for resorption.

In osteoporosis, the radiologist does not give us diagnostic help until the condition is advanced and the histologist can tell us little of pathogenesis. Turning to the biochemists for diagnostic aid, Nordin and Fraser (1954) have described a four-hour skeletal retention of calcium test. The patient is given an intravenous load of calcium gluconate in 500 ml. of normal saline. The amount of calcium retained by the skeleton is derived from a formula which requires the estimation of the level of serum-calcium and of the amount of calcium excreted in the urine. The test has the disadvantages that it takes a day of a chemist's time, if the calcium estimates are done in triplicate, and, if the results are to be valuable, the estimation of serum calcium must be accurate to the first decimal point. It is an attractive investigation for it is a direct measurement of the functional activity of bone; it emphasizes the fact that bone is a living tissue in which changes of protein and calcium content are constantly proceeding. I have used it several times and it has run true for me.

*Case II.*—F. R., a woman aged 60; the menopause was at 42 years, and she had progressively severe back pain for twenty years. X-rays of the spine showed a well-marked osteoporosis with collapse of three of the dorsal vertebræ and of L.1. The serum calcium was normal and the Nordin-Fraser skeletal retention-test gave a value of 41%—the normal range being between 48% and 62%—and, therefore, diminished calcium retention. The specific gravity of the urine after fluid fasts of eighteen to twenty-four hours was invariably 1·008 and 1·009. There was no other

evidence of an abnormal renal function. Throughout the whole experimental period the daily intake of calcium was about 1·3 grams. The urinary calcium was around 200 mg. in twenty-four hours. The urinary volume varied between 2,200 and 2,800 ml. With twenty-onedays' œstrogen therapy the urinary calcium dropped to 71 mg., 92 mg., and 80 mg. in the twenty-four hours. The urinary volumes were reduced by an average of 500 ml. per day; and the specific gravity, after eighteen hours' fluid fasting, rose slowly to 1·013 (Fig. 3).

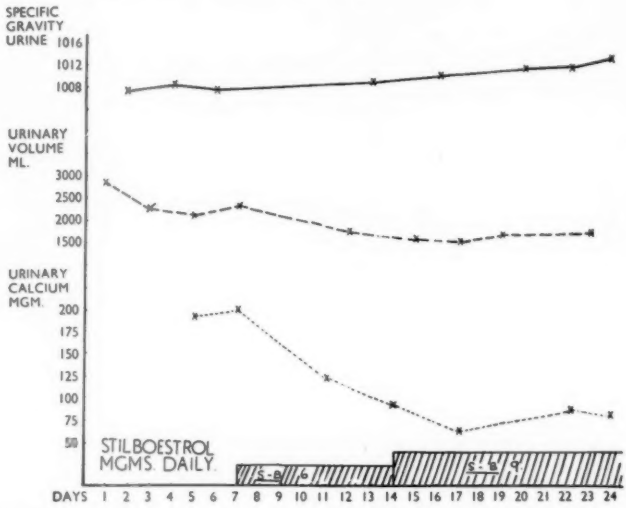



FIG. 3 (*Case II*).—Reduction of urinary calcium excretion and polyuria, and rise in specific gravity of urine in osteoporosis with œstrogen therapy.

The association of polyuria and hypercalciuria are discussed later, but I want to emphasize here the rapidity with which œstrogen therapy diminishes the urinary excretion of calcium. We assume, by analogy with animal experiments, that it does so by encouraging osteoblastic activity, so that the increased deposition of protein matrix requires the retention of calcium.

Androgens also are required in the treatment of several varieties of osteoporosis, and if methyl testosterone produces unpleasant virilizing effects, 17-α-ethyl-19-nortestosterone may be substituted for it.

### *Hyperparathyroidism*

The main diagnostic problems of hyperparathyroidism were explicitly stated by Albright and Reifenstein (1948), and have frequently been exemplified since: The problem of the patient whose skeleton shows resorption but in whom the characterististic radiological features are absent; the problem of the patient with neither hypercalcæmia nor hypophosphatæmia; the problem of the patient in whom there is renal failure which produces hyperphosphatæmia, which itself may lead to a secondary hyperparathyroidism; the problem of the patient without bone changes but with renal calculi; the problem of the patient with no bone changes, but with polyuria and a low specific gravity urine. I repeat that we are familiar enough with these diagnostic situations, but I do not say that we always find them easy of solution.

Let us leave these diagnostic questions aside to consider one or two problems of pathogenesis. How is it, for example, that renal calculi, nephrocalcinosis, or polyuria can occur in the absence of demonstrable bone changes? The hypothesis that there are two parathyroid hormones does not help us for the one is said to act on the bones and the other to enhance phosphate excretion; and we require an explanation for the increased excretion of calcium from bones that yet do not show the lack of it. The explanation usually given, and repeated in Snapper's new book "Bone Diseases in Medical Practice" (1957), is that some take so much milk and vitamin D that the calcium in the bones is easily replaced and the skeleton thus protected. This seems to proffer an unacceptable and superficial explanation, for the action of parathyroid hormone on the skeleton is to increase osteoclastic activity, so that there is not only a loss of calcium but also a loss of protein matrix. Nor is the required explanation that there is a small degree of increased resorption which is not apparent to the radiologist but is detectable by the histologist.

*Case III.*—I was given an "unseen" at a medical-school clinico-pathological conference some months ago. The patient, a woman of 56, had proven thyrotoxicosis but died with an unexplained illness associated with hypercalcæmia, vomiting, dehydration, a low specific gravity urine, and a relative polyuria. Among the lesions discovered at post-mortem were nephrocalcinosis, pyelonephritis and a parathyroid adenoma. The bones of the skull were reported by the pathologist to show no osteitis fibrosa and no enhanced resorption. Is it possible that an increased osteoblastic activity develops in the bones which balances the increased osteoclastic activity?

### *The Polyuria of Hyperparathyroidism*

It has long been appreciated that there is a polyuria in hyperparathyroidism associated with the passage of a low specific gravity urine and that when the parathyroid adenoma is removed the polyuria and polydipsia quickly disappear. Cohen *et al.* (1957) have recently made the important observation that this is due to a functional and reversible lesion of the distal tubule and they ask whether it is a consequence of hyperparathyroidism or of hypercalciuria. I have no doubt that the polyuria is due to the hypercalciuria. I have seen it both in the hypercalcæmia of sarcoidosis and secondary deposits in bone, and seen it disappear quickly after treatment—in the former patient with cortisone therapy and in the latter after oophorectomy. If I am right, this sign will not differentiate hyperparathyroidism from other conditions with hypercalcæmia, but polyuria and a low specific gravity urine are very important bedside-pointers to hyperparathyroidism, and they have twice led me, although somewhat tardily, to a correct diagnosis.

The fourth patient illustrated two areas of diagnostic difficulty—the first where a renal lesion reverses the characteristic biochemical changes, and the second where doubt arises between the differentiation of primary and secondary hyperparathyroidism. Moreover, the post-mortem examination provided ample opportunity for argument to pathologists and physicians as shown below.

*Case IV.*—B. B., a spinster aged 29, and deaf-mute. Height 5 ft. 1 in. In 1954, aged 27, she fell and damaged the left knee. In 1955 she fell and damaged the right knee; and when she presented in 1956 to my colleagues in the Orthopædic Department, Mr. R. G. Pulvertaft and Mr. E. W. O. Adkins, she was suffering from a spontaneous fracture of both quadriceps above the patella—associated with deposits of calcium. She was referred to me for investigation, when X-rays of the skeleton showed generalized osteoporosis, compression deformities in the vertebræ, subperiosteal resorption in the phalanges, advanced arterial calcification, calcium deposits, osteoporosis in the skull with, however, areas of osteosclerosis. The serum calcium had values varying from 10·8 to 11·3 mg./100 ml.; the serum phosphorus varied from 7·8 to 8·9 mg./100 ml.; and the alkaline phosphatase was 35 to 66 units (King-Armstrong). The blood urea was 350 mg./100 ml.; the $CO_2$ combining power was 11 mEq.; the urine contained albumin and casts and was of low specific gravity. She was anæmic (hæmoglobin 6·9 grams, red blood cells 2,500,000). The diagnosis on all counts was not in doubt. She was suffering from renal osteo-dystrophy, associated with parathyroid hyperplasia. She was treated with sodium bicarbonate and small transfusions. She died eight months later in uræmic convulsions. At autopsy the kidneys were found to be small, measuring 8 cm. in length (Fig. 4). They showed glomerular sclerosis, diffuse



FIG. 4 (*Case IV*).—Contracted kidney—8 cm. in length.

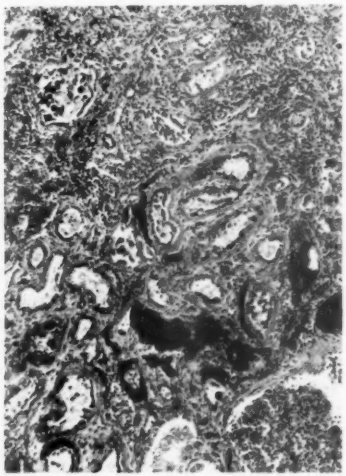


FIG. 5 (*Case IV*).—Kidney ×65, showing glomerulosclerosis, tubular dilatation and calcinosis.



FIG. 6 (*Case IV*).—Parathyroid adenomata, weight (A) 10·5 grams, (B) 1·5 grams.

scarring, and focal calcification (Fig. 5). The bones were the seat of osteitis fibrosa but the parathyroid showed not hyperplasia as I had expected, but adenomata. The larger one, shown on the left, weighed 10·5 grams and the smaller one on the right, which is just discernible, weighed 1·5 grams (Fig. 6). The tumour is composed mainly of sheets of oxyphil and rose-pink cells with the oxyphil cells forming alveolæ.

This report is capable of more than one interpretation. My own conclusion is that the chronic renal lesion was the primary disease; the osteitis fibrosa followed uræmia and chronic acidosis; the parathyroid hyperplasia was secondary to the phosphorus retention and the autonomous functioning parathyroid adenomata developed secondarily to the hyperplasia. This patient suffered first from secondary hyperparathyroidism, and then from primary hyperparathyroidism.

Davies *et al.* (1956) described recently a patient with steatorrhœa and a parathyroid adenoma (weight 150 mg. and composed of chief cells) in whom they concluded that an autonomous parathyroid adenoma had developed secondarily to the hyperplasia which was secondary to the hypocalcæmia of steatorrhœa. In subsequent correspondence Professor Russell Fraser and Dr. Nordin compared this parathyroid adenoma to those that have "already been suggested for the secondary hyperparathyroidism of glomerular failure". Professor Dent replied "We would also appreciate a reference to this happening . . . we have not read this". This patient of mine supplies Professor Dent's missing reference.

The pituitary in this patient "showed considerable hyperplasia of eosinophil cells; basophil and chromophobe cells are relatively inconspicuous" (Dr. G. R. Osborn). The problem case at the clinico-pathological conference had "a large right lobe in the hypophysis containing almost exclusively eosinophilic cells; though not encapsulated there was present an eosinophilic 'adenoma' of 7–8 mm. in diameter" (Professor D. H. Collins).

Does this eosinophilic excess represent a homœostatic attempt by the growth hormone to provide an increased osteoblastic activity to balance the osteoclastic excess; sometimes thereby achieving an equilibrium, sometimes losing the bony battle, but occasionally obtaining a local success, as in renal osteodystrophy by the production of osteosclerosis?

I am grateful to Professor Graham Wilson and Professor D. H. Collins for permission to make reference to Case III, and to Dr. G. R. Osborn for the pathological reports in Case IV.

## REFERENCES

ALBRIGHT, F. (1943) *Harvey Lect.*, **38**, 123.
——, and REIFENSTEIN, E. C. (1948) The Parathyroid Glands and Metabolic Bone Disease. Baltimore; p. 166.
BABAIANTZ, L. (1948) *J. Radiol. Électrol.*, **29**, 333.
COHEN, S. I., FITZGERALD, M. G., FOURMAN, P., GRIFFITHS, W. J., and DE WARDENER, H. E. (1957) *Quart. J. Med.*, **26**, 423.
DAVIES, D. R., DENT, C. E., and WILCOX, A. (1956) *Brit. med. J.*, ii, 1133.
FRASER, T. R. C., and NORDIN, B. E. C. (1956) *Brit. med. J.*, ii, 1363.
HEWITT, D., WESTROPP, K., and ACHESON, R. M. (1955) *Brit. J. prev. soc. Med.*, **9**, 179.
NORDIN, B. E. C., and FRASER, R. (1954) *Clin. Sci.*, **13**, 477.
SNAPPER, I. (1957) Bone Diseases in Medical Practice. New York and London.

**Dr. R. E. Steiner** (London):

In systemic general disease radiological manifestations affecting the skeleton are common. For practical purposes it is best to divide the appearances into two main groups.

(A) Conditions which are manifested by a decrease in bone density, as, for example, osteoporosis, osteomalacia, and hyperparathyroidism.

(B) Conditions manifested by an increase in bone density such as myelosclerosis, fluorosis, or sclerosing metastases.

In both groups the general radiological appearance may be quite similar in a number of different diseases; however, specific manifestations may also be present which at times help to distinguish individual conditions.

The radiological assessment of bone density depends largely on the observer's own experience. No scientific absolute methods are available to measure bone density. Comparison with normal bone standards is of help, particularly in the small bones of the hands and feet, where overlying soft tissues are of relatively little importance. In the assessment of large bones, particularly the spine, the same does not apply for obvious reasons. Additional factors which must always be considered in assessing bone density are the wide normal variations dependent on age, sex, and body-build.

As a rule when one assesses bone density on standard radiographs, one should observe the width and density of the cortex and compare it with the appearance of the trabecular medullary bone density and the amount of spongiosa relative to the cortex. It can be seen that the ratio of cortex to medulla is fairly constant in normal bones; whereas in bones with decreased density the cortex appears thin and narrowed and the spongiosa mass

appears more extensive with thinning of individual bone trabeculæ. This is best observed in the long shaft bones. Conversely in dense bones, the cortex appears to be thickened and dense. The spongiosa mass appears to be diminished and individual bone trabeculæ are thicker and denser.

In a radiological survey of the skeleton X-ray films should be limited to a reasonable number. It is necessary to radiograph a few selected areas only for adequate assessment, quite apart from the undesirability of unnecessary exposure to radiation in view of its potential hazards. The following projections are suggested as adequate for a routine survey:

(1) A.P. projections of the hands and feet; if possible a normal bone standard, as for example, a metacarpal should be included on this film.
(2) One projection of a large long bone, i.e. a femur or humerus.
(3) A.P. projection of pelvis.
(4) A lateral film of the dorsi-lumbar spine.
(5) A lateral radiograph of the skull.

A radiograph of the chest will give some additional information on the bony structures of the thoracic cage.

It is the purpose of this communication to confine the discussion to a few specific conditions such as osteoporosis, osteomalacia and hyperparathyroidism and only briefly to mention the other conditions associated with skeletal manifestations of general disease.

## A. Conditions Giving Rise to Decreased Bone Density

The radiological feature which is common to osteoporosis due to defective matrix, or osteomalacia due to defective calcification of the skeleton, or extensive bone destruction due to hyperparathyroidism, is a generalized decrease in bone density which may be associated with skeletal deformities or fractures indicating generalized bone softening (Table I).

Table I.—Bones with Decreased Density (Thin Bones)

(1) *Osteoporosis:*
  *a* Senile, *b* Pregnancy, *c* Disuse, *d* Hyperthyroidism, *e* Cushing's syndrome, *f* Steroid therapy, *g* Acromegaly, *h* Malnutrition, *i* Hypervitaminosis D (soft tissue calcification)
(2) *Osteomalacia and rickets:*
  *a* Vitamin-D deficiency
  *b* Steatorrhœa
  *c* Renal tubular defects
  *d* Chronic uræmia (late)
(3) *Hyperparathyroidism:*
  (1) Primary
  (2) Secondary
    *a* Renal tubular defects
    *b* Chronic uræmia
    *c* Osteomalacia (late)

### *Osteoporosis*

Generalized osteoporosis irrespective of its many causes, is characterized by a diffuse decrease in bone density affecting at first the axial skeleton such as the spine, pelvis, and large long bones; in the advanced stage the smaller peripheral bones may also be involved. The bony cortex appears thin, the trabeculæ of the medulla are thin and narrowed and if this becomes extreme only a "ghost-like" outline of the bony pattern may be visible. Fractures involving the vertebral bodies are common, particularly in the dorsilumbar region. Fractures affecting the long bones are unusual, and the so-called "stress fracture" or Looser zones which occur in osteomalacia are never seen. In view of the softening of bone there may be appreciable deformity of the spine, such as kyphoscoliosis; the intervertebral spaces are widened due to prolapse of the intervertebral discs into the softened vertebral bodies.

The above description is usually seen in senile osteoporosis or idiopathic osteoporosis aggravated by pregnancy or malnutrition.

In Cushing's syndrome osteoporosis is not a constant feature; fractures are occasionally present, particularly of the ribs and vertebral bodies (Albright and Reifenstein, 1948). Prolonged steroid therapy may produce a radiological picture similar to that seen in Cushing's syndrome with osteoporosis and fractures (*British Medical Journal*, 1955).

In hypervitaminosis D severe osteoporosis can occur, but this may be overshadowed by extensive metastatic soft tissue calcifications which can affect a number of organs, such as the heart, lungs, kidneys, subcutaneous tissue, muscles, blood vessels, and synovial

membranes (Christensen *et al.*, 1951). In view of this combination of soft tissue metastatic calcification and the marked underlying osteoporosis a differential diagnosis from skeletal manifestations due to chronic renal failure and secondary hyperparathyroidism, may at times be difficult.

*Osteomalacia*

The main skeletal manifestation in osteomalacia is a generalized decrease in bone density of the skeleton, frequently associated with considerable deformity. The pelvis may be flattened giving rise to the characteristic triradiate appearance, vertebral bodies are collapsed with bi-concave articular surfaces so-called "fish-tailed" vertebræ. Associated with this there is considerable widening of the intervertebral spaces with intervertebral discs prolapsing into the softened vertebral bodies as in osteoporosis (Fig. 1). There may

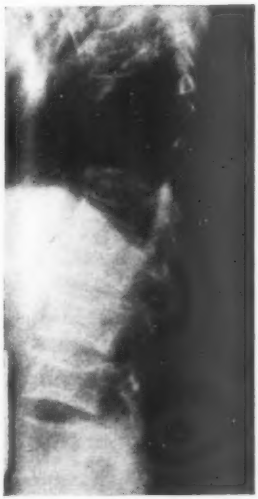


FIG. 1.—Lateral radiograph of the dorsilumbar spine. Female with osteomalacia due to steatorrhœa. This film demonstrates vertebral collapse and widened intervertebral spaces.



FIG. 2.—A.P. radiograph of the pelvis. Female with vitamin-D-resistant osteomalacia. This film demonstrates triradiate deformity of the pelvis. Looser zones right upper femur, pubic bones and right ilium.

be bowing of long bones particularly the lower limbs and there may be basal invagination of the skull. Another less common but more specific feature is the pseudo-fracture or Looser's zone. These fractures may only involve the cortex; rarely do they appear as a complete fracture across the whole width of the bone. They are often symmetrical; occur at points of stress or where large nutrient foramina enter the bone (Le May and Blunt, 1949) (Fig. 2). Common sites for these fractures are pubic rami, iliac crests, scapular borders, ribs, and shafts of the long bones. These stress fractures occur typically in osteomalacia (Albright and Reifenstein, 1948) and do not occur in osteoporosis.

Dent and Hodson (1954) consider that there are two types of osteomalacia. The more chronic where there is marked decrease in bone density and deformity of the skeleton, and the more acute where there may be little evidence of decrease in bone density, but Looser zones are present. Looser zones heal readily with treatment of the underlying condition.

In osteomalacia due to renal tubular defects, chronic uræmia, and steatorrhœa, there may be evidence of secondary hyperparathyroidism.

*Bone Changes in Chronic Renal Failure* (*Renal Osteodystrophy*)

The radiological appearance in renal osteodystrophy tends to be varied. Frequently a number of different lesions are present in the same case. The following manifestations can be recognized:

(1) In the young and growing patient there will be evidence of retardation of growth and

ossification associated with epiphyseal and metaphyseal changes indistinguishable from juvenile rickets with marked decrease in bone density (Snapper, 1949; Claireaux, 1953).

(2) In the adult there is occasionally evidence of minor degrees of osteomalacia (Follis, 1950).

(3) Most commonly there is evidence of secondary hyperparathyroidism manifested by the presence of subperiosteal cortical erosions in the phalanges, the terminal tufts of the digits (Fig. 3) and along the cortex of the long bones near joints (Pugh, 1951; Dent and



FIG. 3.—Radiograph of a digit. Young male with renal osteodystrophy. Marked cortical erosions in the phalanges and of the terminal phalangeal tuft.



FIG. 4.—Lateral radiograph of the dorsal spine. Young male with renal osteodystrophy. Note the marked sclerosis of the vertebral bodies.

Hodson, 1954). There may be evidence of slight decrease in bone density with characteristic mottled appearance of the bones of the vault of the skull. Cyst formation which occurs in primary hyperparathyroidism is most unusual in secondary hyperparathyroidism. There may be considerable bone destruction of the ends of the long bones near the metaphysis with considerable thinning of bony trabeculæ (Gilmour, 1947; Albright and Reifenstein, 1948; Follis, 1950).

(4) Rarely there is evidence of sclerosis of the skeleton affecting mainly the vertebral bodies (Fig. 4), vault of the skull and the shafts of the long bones (Crawford *et al.*, 1954; Wolf and Denko, 1958). Sclerosis of the skeleton is probably the most chronic manifestation of renal osteodystrophy.

Metastatic calcifications are frequently seen in chronic renal failure, arteries are affected including the small digital vessels and so is the muscular and subcutaneous tissue. On the plain radiograph of the abdomen renal shadows may appear small and shrunken and there is frequent evidence of nephrocalcinosis.

### *Hyperparathyroidism*

*Primary hyperparathyroidism.*—The radiological presentation of primary hyperparathyroidism is often as bizarre and varied as are clinical manifestations. The most important sign is evidence of subperiosteal cortical erosions in the shafts of the long bones and considerable bone absorption. This is best seen in the phalanges of the hands and feet and in the shafts of the long bones near large joints. There may be bony changes in the vault of the skull giving it a rather woolly mottled appearance (Figs. 5 and 6). In the advanced case there may be generalized decrease in bone density. This can be very marked and often associated with considerable deformity of the skeleton and pathological fractures. Bone cysts are quite common. They usually occur in the shafts of the long bones, ribs,



FIG. 5.—Lateral radiograph of the skull. Female with primary hyperparathyroidism. Note the woolly appearance of the vault of the skull.



FIG. 6.—Same patient eight weeks after the removal of the parathyroid adenoma. The vault is completely recalcified and appears normal.

or the mandible where they can be very large and may be indistinguishable from osteoclastoma.

Frequently, however, the skeletal appearance may be normal (Albright and Reifenstein, 1948).

The only abnormal feature may be evidence of renal calculi. Barium swallow can at times localize a parathyroid tumour in the neck. It may be possible to identify it as a vascular tumour by arteriography (Steiner *et al.*, 1956).

Post-operatively bone repair and recalcification of the skeleton takes place within months but it may be years before it is complete (Albright and Reifenstein, 1948).

*Secondary hyperparathyroidism.*—Secondary hyperparathyroidism can occur in chronic uræmia, renal tubular defects, and late in osteomalacia. The radiological manifestations on the whole are indistinguishable from primary hyperparathyroidism; however, the occurrence of bone cysts is rare, but metastatic calcifications are common in blood vessels, muscle and subcutaneous tissue.

*Decreased Bone Density due to Bone Replacement*

A large number of conditions will produce decreased bone density; some of the more important are listed in Table II. Lesions can either produce localized manifestations of

TABLE II.—BONES WITH DECREASED DENSITY (THIN BONES)

(4) *Bone replacement:*
- *a* Secondary carcinoma
- *b* Myelomatosis
- *c* Reticulo-endothelial disorders
- *d* Blood diseases
- *e* Lipoidosis
- *f* Urticaria pigmentosa
- *g* Localized fibrocystic diseases

bone translucency, as, for instance, a solitary secondary deposit, or they can be very much more widespread as in myelomatosis or the various lipoid disorders. Rarely are they so generalized and widespread that they may produce a more or less uniform radiological picture of decreased bone density (Fig. 7) simulating the conditions listed in Table I.



FIG. 7.—Radiograph of the upper end of the femur. Patient with advanced myelomatosis. This film demonstrates marked hypertranslucency of the bone, with thinning and slight scalloping of the cortex, and an excessively wide and hypertranslucent medulla.

B. CONDITIONS GIVING RISE TO INCREASED BONE DENSITY

Some of the more important groups of conditions are listed in Table III. The general

TABLE III.—BONES WITH INCREASED DENSITY

(1) *Secondary deposits:*

(2) *Endocrine and metabolic disorders:*
- *a* Sclerotic renal osteodystrophy
- *b* Hypervitaminosis A

(3) *Poisons:*
- *a* Lead
- *b* Fluorosis
- *c* Bismuth
- *d* Radium

(4) *Unknown Ætiology:*
- *a* Paget's disease
- *b* Myelosclerosis
- *c* Idiopathic hypercalcæmia
- *d* Hypertrophic pulmonary osteoarthropathy

considerations discussed before also apply to these groups. The manifestations can b

(1) Localized or patchy, such as sclerotic secondary deposits where bone sclerosis occurs in response to stimulus from a secondary growth.

(2) Lesions may be more generalized affecting the whole skeleton more or less uniformly as, for example, in myelosclerosis (Fig. 8) or fluorosis.

(3) Increased bone density may be mimicked by periosteal new bone formation without underlying bone sclerosis as in hypertrophic pulmonary osteoarthropathy (Fig. 9).



FIG. 8.—Radiograph of the pelvis. Male, with myelosclerosis. The bones of the pelvis and femoral shafts show loss of translucency with a homogeneous appearance making distinction of cortex and medulla impossible.



FIG. 9.—Radiograph of the femur. Young boy with congenital agranulocytosis and chronic pulmonary suppuration, who developed severe hypertrophic pulmonary osteoarthropathy. There is very marked periosteal new bone formation producing loss of translucency in the region of the mid-shaft of the femur. NOTE: the other long bones of the skeleton were equally affected.

## REFERENCES


ALBRIGHT, F., and REIFENSTEIN, E. C. (1948) The Parathyroid Glands and Metabolic Bone Disease. Baltimore.

*British Medical Journal* (1955) i, 278.

CHRISTENSEN, W. R., LIEBMAN, C., and SOSMAN, M. C. (1951) *Amer. J. Roentgenol.*, **65**, 27.

CLAIREAUX, A. E. (1953) *J. Path. Bact.*, **65**, 291.

CRAWFORD, T., DENT, C. E., LUCAS, P., MARTIN, N. H., and NASSIM, J. R. (1954) *Lancet*, ii, 981.

DENT, C. E., and HODSON, C. J. (1954) *Brit. J. Radiol.*, **27**, 605.

FOLLIS, R. H., Jr. (1950) *Bull. Johns Hopk. Hosp.*, **87**, 593.

GILMOUR, J. R. (1947) The Parathyroid Glands and Skeleton in Renal Disease. London.

LE MAY, M., and BLUNT, J. W., Jr. (1949) *J. clin. Invest.*, **28**, 521.

PUGH, D. G. (1951) *Amer. J. Roentgenol.*, **66**, 577.

SNAPPER, I. (1949) Medical Clinics on Bone Diseases. 2nd ed. New York.

STEINER, R. E., FRASER, R., and AIRD, I. (1956) *Brit. med. J.*, ii, 400.

WOLF, H. L., and DENKO, J. V. (1958) *Amer. J. med. Sci.*, **235**, 33.


**Dr H. A. Sissons** (London):

*Histological Changes Encountered in Some Generalized Skeletal Diseases*

In the adult skeleton, the structural changes usually associated with metabolic bone disease are osteoporosis, osteomalacia and "osteitis fibrosa". The present paper describes each of these in order to show how they are related to the radiological findings, as already outlined by Dr. Steiner. The abnormalities of the child's skeleton, where rickets is the counterpart of osteomalacia, and where abnormalities of growth are of great importance, will not be discussed.

*In osteoporosis* (Sissons, 1955) the structural abnormality is a reduction in the amount of bone tissue, without any defect in its mineralization. Interest centres, from the cellular point of view, on its mechanism of production. The normal skeleton is the result of continuously active but balanced bone destruction and bone formation: reduction in the amount of skeletal tissue can follow either an increase in bone destruction or a decrease in bone formation, and there is evidence that sometimes one and sometimes the other can be concerned in osteoporosis. It is also possible that "turnover" of skeletal tissue might be stabilized with a reduced amount of such tissue present: this would represent osteoporosis at a non-progressive stage. Difficulties in the independent assessment of these two cellular processes, whether by structural or physiological methods, make it difficult to be dogmatic regarding the precise mechanism concerned in any particular clinical variety of osteoporosis.

Gross degrees of osteoporosis can be easily recognized histologically, for instance in biopsy material, but the absence of quantitative information on the normal range of skeletal structure in various situations makes the histological recognition of minor degrees of osteoporosis uncertain.

*Osteomalacia.*—Here the structural abnormality is the presence of an excessive amount of osteoid tissue (i.e. non-calcified bone matrix) in the skeleton, this being the result of failure of calcification of the tissue and not of any selective removal of bone salt from calcified tissue ("halisteresis"). It is a condition which rarely comes to the attention of the diagnostic histologist; when it does, its recognition depends on certain technical procedures for the identification of osteoid tissue—that is to say its distinction from calcified bone. There are three of these methods:

(1) Demonstration of bone salt in undecalcified sections by treatment with silver nitrate solution (the von Kossa technique—*see* Ball, 1957). Osteoid tissue appears pale in contrast to the blackened calcified bone (*see* Fig. 1). The disadvantage of the technique is that the sections tend to fragment: in any case it can be applied only to cancellous bone.



FIG. 1 (×43).—Von Kossa preparation of undecalcified osteomalacic bone, showing large amounts of osteoid tissue.



FIG. 2 (×79).—Hæmatoxylin and eosin stained preparation of bone decalcified with neutral E.D.T.A. (Ethylene diamine tetra-acetic acid).

(2) Differential hæmatoxylin staining of calcified bone and osteoid tissue in decalcified material is the method usually employed in diagnostic work: its efficacy following various decalcifying agents has been reviewed by Meyer (1956). It appears to be an adequate method if decalcification and staining are carefully performed. Osteoid tissue appears pale (or pink if counterstained with eosin), while calcified bone tissue stains blue (*see* Fig. 2).

(3) As a research technique, the X-ray absorption of ground preparations of undecalcified bone can be used (*see* Meyer, 1956) to determine whether or not particular areas of tissue are calcified. In microradiographs, osteoid tissue fails to show any X-ray absorption, but it is evident when the preparation is examined by transmitted light (*see* Figs. 3, 4). The technique is rigorous in its specificity and can be applied to any type of bone tissue, but it entails the use of specialized equipment for tissue grinding and microradiography.



FIG. 3 (×33).—Undecalcified ground preparation of rachitic bone viewed by transmitted light. Osteoid tissue appears as a paler layer on the surface of the bony trabeculæ.

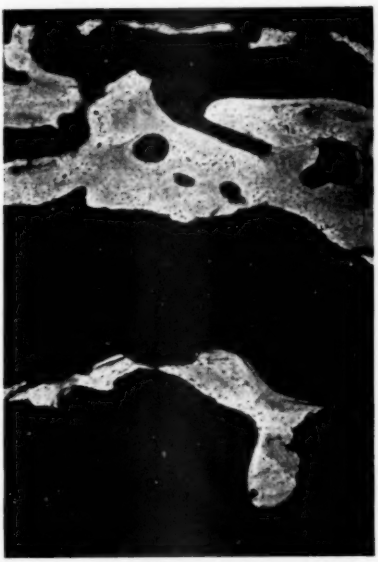


FIG. 4 (×33).—The area of tissue shown in Fig. 3, as seen in a microradiograph. The calcified bone tissue has absorbed X-rays, but no shadow is produced by the non-calcified osteoid borders.

With the proper use of one or other of these techniques, there should be no difficulty in recognizing excessive amounts of osteoid tissue with certainty in biopsy or post-mortem material.

*Osteitis fibrosa.*—What we now know as "osteitis fibrosa" was originally lumped by von Recklinghausen (1891), with a variety of other conditions, under the term "generalized osteitis fibrosa cystica". Subsequently it had been distinguished from other forms of bone fibrosis now known by other names, including fibrous dysplasia and the various cysts and "fibromas" encountered in bone. This separation was effected by a number of workers, but I would particularly like to refer to the work of Hunter and Turnbull (1931) in sorting out two types of "generalized osteitis fibrosa". The first of these consists of multiple circumscribed lesions, is not associated with parathyroid disease and is now known as fibrous dysplasia of bone. The second type, recognized by its diffuseness, is associated with hyperparathyroidism: it is what we now know as "osteitis fibrosa", and is encountered in primary hyperparathyroidism, and also in prolonged renal failure, when it is thought to be due to secondary hyperparathyroidism. The clinical problem of distinguishing between the end-results of primary and secondary hyperparathyroidism is sometimes difficult in the skeletal lesions; "brown tumours" and "cysts" appear to be features of the primary condition, while excessive amounts of osteoid tissue and abnormal structural architecture of bone are sometimes observed in "renal osteodystrophy".

In order to illustrate the range of bone changes encountered in renal failure, I shall contrast two cases, each the aftermath of chronic pyelonephritis and each associated with uræmia of some years' duration—with acidosis, phosphate retention and a lowered serum calcium. One case failed to show any detectable radiological abnormality during life, and

at autopsy the skeleton showed only minimal osteitis fibrosa (Figs. 5, 6) with scattered areas of osteoclastic resorption of bone and fibrous tissue replacement. Although the general clinical features and biochemical abnormalities of the other case were very similar, it showed conspicuous radiological changes of the type illustrated by Dr. Steiner (Figs. 3 and 4, *see* p. 482), involving skull, fingers, femora, spine and showing transverse banding of vertebral bodies. The radiological appearances are clarified by Figs. 7 and 8, which show



FIG. 5 (×2).—Minimal osteitis fibrosa. X-ray of a slab of cancellous bone from the upper part of the femur, showing the "hollowed" appearance of many bone trabeculæ.

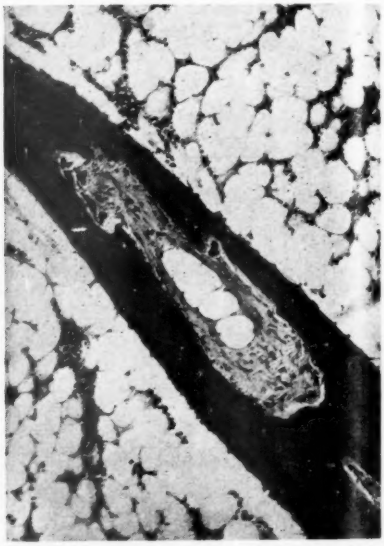


FIG. 6 (×76).—A photomicrograph from the area illustrated in Fig. 5, showing the histological appearance of a trabecula hollowed by osteoclastic erosion and fibrous tissue replacement.



FIG. 7 (×2).—Extreme renal osteodystrophy. X-ray of a slab of bone of a lumbar vertebral body showing the abnormal arrangement of bony structures.

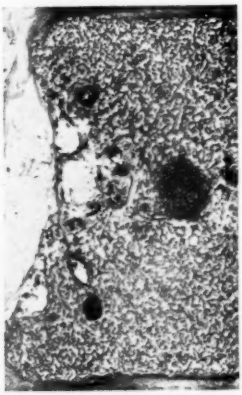


FIG. 8 (×2).—A photomicrograph from a lumbar vertebra similar to that in Fig. 7, showing fibrous replacement and general repatterning of bone.

the extreme structural rearrangement of bony architecture present. In addition to exaggerated osteoclasis and fibrous replacement of bone, complete "repatterning" of the

bony architecture has occurred, the cancellous bone of the vertebral body consisting of very numerous thin and irregular trabeculæ. These structures are "woven" bone, and not the "lamellar" bone present in the normal skeleton. The lattice-work of these abnormal bone trabeculæ is closer at the upper and lower surfaces of the vertebral body than in the centre, and this is responsible for the banded appearance in the clinical radiographs.

## REFERENCES


BALL J. (1957) *J. clin. Path.*, **10**, 281.
HUNTER, D., and TURNBULL, H. M. (1931) *Brit. J. Surg.*, **19**, 203.
MEYER, P. C. (1956) *J. Path. Bact.*, **71**, 325.
RECKLINGHAUSEN, F. D. von (1891) In: Festschrift. Rudolf Virchow. Berlin; p. 131.
SISSONS, H. A. (1955) *Proc. R. Soc. Med.*, **48**, 566.


**Dr. C. E. Dent and Miss Christine M. Harper (London):**

*Hypoparathyroid Tetany (following Thyroidectomy) Apparently Resistant to Vitamin D*

Miss F. C., aged 43, was referred to us by Dr. J. A. Robertson on account of severe tetany. When first seen by him in September 1956 she gave a four to five-year history suggestive of thyrotoxicosis which had recently become severe and unambiguous. Treatment with carbimazole had little effect so she was treated on November 5, 1956, by subtotal thyroidectomy. The operation was difficult and she was believed to have lost most of her thyroid gland. From November 23, 1956, she was given thyroid ½ grain t.d.s. On December 1 and 2 she developed epileptic convulsions and on examination other signs of tetany were elicited. On December 3 her serum calcium was 4·2 mg.%, phosphorus 6·7. Treatment was begun with large doses of calcium gluconate (4 grams q.d.s.) and of calciferol (10 mg. or 400,000 i.u. daily) and on December 6, as her tetany was unchanged, she was given in addition A.T.10 10 ml. (12·5 mg.) daily. By December 20 no appreciable change in her symptoms or plasma had occurred. Arrangements were therefore made to change from the A.T.10 to pure dihydrotachysterol (DHT) 8 mg. daily, slowly lowering this to 4 mg., but this still had no effect. At this stage (December 27, 1956) she was transferred to the Metabolic Ward (U.C.H.) for full study.

She was now given 6 mg. daily of DHT and after the usual equilibration period, calcium and phosphorus balance determinations were begun. At the same time renal function tests and fat balance determinations were done, with normal results, thus excluding known causes which raise the requirement of vitamin D. Skeletal X-rays showed only minimal osteoporosis. Some of the results are shown in Fig. 1. They readily explain her apparent

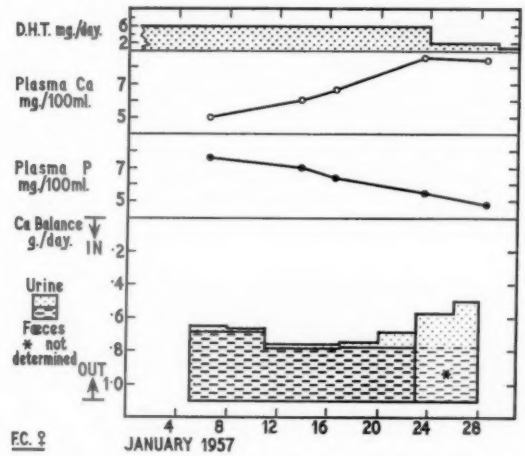



FIG. 1.—Metabolic data on Miss F. C. The calcium balance shown on the lower part is charted so that the dietary intake of calcium (1·1 grams) is measured downwards from the zero line and the outputs in the fæces and urine upwards. The positive balance (0·6–0·7 gram/day) is therefore shown as the space above the blocks for fæcal and urinary output and below the zero line.

"resistance" to the enormous doses of vitamin-D preparations given till then. It is seen that she was in very strongly positive calcium balance at first, with very low fæcal output. Her positive phosphorus balance (not shown) was about half her positive calcium balance. This means that the DHT was indeed acting quite satisfactorily, but that she had a "hungry bones" phenomenon whereby the calcium absorbed from the diet was going straight into her bones without raising her plasma level. It is noted that her calcium balance became less positive and her plasma level and urine calcium rose slowly while under observation. Clearly her bones were by then nearly fully reconstituted, and as further proof of this we were soon able gradually to reduce her dose of DHT while still maintaining normal plasma levels. In June 1957 she was having only 1 mg. b.d., and her plasma showed calcium 9·1, phosphorus 5·6, phosphatase 9.

A similar case has been described by Blohm *et al.* (1953), although a detailed study was not made. In most cases of thyrotoxicosis the osteoporosis is not severe and the tetany which so often follows treatment by partial thyroidectomy is due only to a temporary dysfunction of the damaged parathyroid glands and is therefore readily cured with relatively small doses of vitamin D (1–2 mg. daily of calciferol or of DHT). In our case, however, an additional feature was present (a rapidly re-growing skeleton) which temporarily aggravated the state of calcium depletion in the body fluids. This is similar to the situation well known to follow removal of a parathyroid tumour in such cases as show much skeletal involvement. It is of interest that our patient had at first slightly raised alkaline phosphatase levels (15 K-A units), which gradually fell as the calcium balance became less positive and the DHT requirement fell. Perhaps in future cases this may indicate the true state of affairs without any need for full metabolic studies. We would now advise treatment with high calcium and vitamin D intakes and, if still intractable, the tetany could presumably be lessened by giving for a while rather large doses of thyroxin (or better, perhaps, tri-iodothyronine) thus allowing the skeleton to re-constitute itself at a slower and more suitable pace.

REFERENCE

BLOHM, R. W., WURL, O. A., GILLESPIE, J. O., and ESCAMILLA, R. F. (1953) *J. clin. Endocrin.*, **13**, 519.

---

## NOTICE

---

### SYMPOSIUM AT THE ROYAL SOCIETY OF MEDICINE

*TO BE HELD ON FRIDAY, OCTOBER 31, 1958*

**DISORDERS OF THE SMALL INTESTINE (EXCLUDING THE DUODENUM)**

Admission by ticket only. Application may now be made to the Assistant Secretar

# Section of Pathology

President—Professor J. W. S. BLACKLOCK, M.D.

[*February* 4, 1958]

## The Role of Fungi as Human Pathogens

By R. W. RIDDELL, M.D., F.R.C.P.Ed.
*London*

ONLY very few species of fungi occurring in nature as saprophytes have the ability to produce infection in man and animals; greater numbers have the ability to evoke allergic reactions in hypersensitive subjects. There are a few fungi like *Malassezia furfur*, causing pityriasis versicolor, and *Blastomyces dermatitidis*, responsible for blastomycosis, which have not been found other than in association with infections of man and animals, but the majority of pathogenic fungi may exist as saprophytes in nature. One of the more recent to be demonstrated in the soil is a ringworm fungus, *Microsporum gypseum*. In the case of the filamentous fungus, *Aspergillus fumigatus*, there is no difference in structure between the saprophytic and parasitic forms of the organism, but in most other pathogenic fungi these forms are dissimilar. In some, such as the fungi causing ringworm, Madura disease and chromoblastomycosis, the parasitic growth represents a restricted or dysgonic form. In others, like *Sporotrichum schencki* and *Histoplasma capsulatum* producing sporotrichosis and histoplasmosis respectively, the parasitic form is entirely different from the saprophytic, and, in consequence, they are termed "dimorphic". The filamentous fungi, therefore, exhibit a range of structural adaptations to parasitic existence; the more adaptable they are the greater is their ability to invade. Some can persist as filamentous organisms in exudates and in non-viable tissues as is the case with *Aspergillus fumigatus* and the dermatophytes or ringworm fungi. At the other extreme, the filamentous form of fungi causing systemic infections is incompatible with parasitism and a change to a unicellular fungal form results (e.g. *H. capsulatum*). A fungus like *Cryptococcus neoformans*, causing torulosis, which exists entirely in a yeast form, is structurally similar in its role as a human pathogen (Fig. 1) and as a saprophyte grown from the soil.

Like all parasites, there is great variability in the amount of injury which fungi inflict on their human or animal hosts. Certain anthropophilic ringworm organisms (e.g. *Epidermophyton floccosum*) growing on the skin surface may remain unnoticed by the host and behave as little more than saprophytes in keratin. Some would query whether the presence of fungus in skin is compatible with normal appearances, but there is no doubt that only the slightest degree of hyperkeratosis may be evoked. In other instances, however, as frequently occurs with the zoophilic ringworm species, the host tissues are injured greatly leading to suppuration and even permanent scarring. Though there tends to be a typical response to infection by various ringworm species, unusual reactions not infrequently occur (Partridge, 1952). It should be stressed that whether or not the host is injured the zone of dermatophyte invasion is always limited to the keratin layer. Living tissues are not attacked by the dermatophyte fungi. Similarly, the wall of a pulmonary cavity or an infected pleural space may be temporarily invaded by *A. fumigatus* without causing apparent harm. On the other hand, an infection of this kind may, in other instances, materially delay healing and give rise to signs and symptoms of toxæmia. Here again, histological examination of the infected areas shows no evidence of fungal invasion of living tissues.

In ringworm and in *A. fumigatus* infections of man, the products of fungi growing in non-viable tissues must be assumed to diffuse into living tissues in the environment, there to

evoke an inflammatory reaction of greater or lesser degree or to bring about tissue degeneration. In some instances it appears that the damage produced in the tissues by fungus "toxins" may pave the way to further fungus invasion; this seems to be the case in aspergillosis, particularly in avian disease. The nature of the toxic products from fungi which produce the changes typifying these various infections has received little study. Henrici (1939) produced evidence for the existence of a thermolabile endotoxin from *A. fumigatus*, and Winner (1956) of a toxin responsible for the pathogenicity of *Candida albicans*. Histologically the lesions of coccidioidomycosis and tuberculosis are closely similar and it is obvious that *Coccidioides immitis* possesses chemical components which evoke caseation in the tissues like that produced by *Myco. tuberculosis*, but these have not been characterized.

As in many other diseases, the factors predisposing to fungal infections are not understood. Obvious causes such as maceration in ringworm infection, and diabetes and antibiotic therapy in moniliasis, are well recognized. Where such factors are absent, as is usually the case, more fundamental reasons for predisposition to infection remain unrecognized. These are particularly pertinent in *Trichophyton rubrum* infections where individual susceptibility to fungal infection, and indeed regional susceptibility too, is very prominent. Differences in host species behaviour are evident in aspergillosis, in which tissue damage from infective, neoplastic or vascular causes is apparently a pre-requisite for human disease, whereas in birds primary infection of healthy tissues may occur. Once infection is established, it is possible that changes occurring in the tissues may promote further fungus invasion. This would seem to be the case in avian aspergillosis where the growth of *A. fumigatus* is intimately associated with an extending area of necrosis (Fig. 2). To a lesser degree this also appears to occur in man, and the extensive invasion of infarcted areas of lung by *A. fumigatus* is evidence of the suitability of non-viable tissues for growth of this fungus.

Of the many aspergillus species only *A. fumigatus* possesses any definite pathogenicity for human tissues, and *C. albicans* is also alone in this respect amongst the numerous candida species (Dawkins *et al.*, 1953). Pathogenicity is, therefore, in these species related to special products of fungal metabolism rather than to structure. All species of microsporum, trichophyton and epidermophyton have the ability to invade keratin, a property dependent on possession of one or more keratinolytic enzymes. The properties of such enzymes remain undiscovered. Within these genera, species differ in their potentialities for attacking keratin of nail and of hair, and in the case of hair such differences may be demonstrated *in vitro* (Fig. 3). Though it is possible to exemplify keratinolysis of hair *in vitro*, the manner in which hair is invaded in such tests is quite different from that which occurs *in vivo*. In natural disease, longitudinal tunnelling of hair occurs always in the direction of the hair bulb. This chemotactic attraction in the direction of germinal cells is obvious, not only in hairs where the advancing line of fungal filaments has long been recognized as Adamson's fringe, but also in skin where dermatophyte hyphæ are seen near to the stratum granulosum of the epidermis (Fig. 4). This invasion of the deeper keratin layers occurring in subjects in whom little tissue response is provoked results in persistence of infection. Under such conditions keratin is attacked as fast as it matures in a zone which is inaccessible to any fungicidal agents known at present.

As in all infections, establishment of mycotic disease depends on the susceptibility of the host and on the infectiveness and virulence of the causative fungus. In torulosis, the fact that laboratory infections are unknown indicates that *C. neoformans* has a low degree of infectivity; torulosis is, furthermore, an uncommon sporadic disease widely distributed throughout the world. Individual proneness to respiratory infection by inhalation would seem to be the all-important factor in this disease. Once established, the fungus may remain localized to lungs or may disseminate when it is usually lethal. As far as can be assessed at present, benign infection is more rare than systemic disease. In coccidioidomycosis and histoplasmosis, on the other hand, infectiveness of the causative fungi is very high, but human susceptibility is such that disease is usually benign and limited to the lungs, only very rarely disseminating.

The fungi pathogenic for man which parasitize in the filamentous form are almost invariably only locally invasive. Some, like *M. audouini* and *T. rubrum*, are usually ideal parasites since they cause negligible harm to the host and are difficult to eradicate. Others, like *T. verrucosum*, are usually unsuccessful parasites in that they evoke a tissue reaction which rapidly brings to an end their existence in keratin. Even less successful parasites are the fungi causing systemic mycoses, for these produce a short-lasting benign infection in which the fungus is destroyed, or more rarely a disseminated infection in which the host perishes. *Aspergillus fumigatus* is dependent on previous lung damage before it can be established in human tissues but it may be responsible for pathological changes at present unassessed. Greater understanding of these infections requires research into the properties of metabolic products of fungal growth and more critical studies of the relationship of various fungus

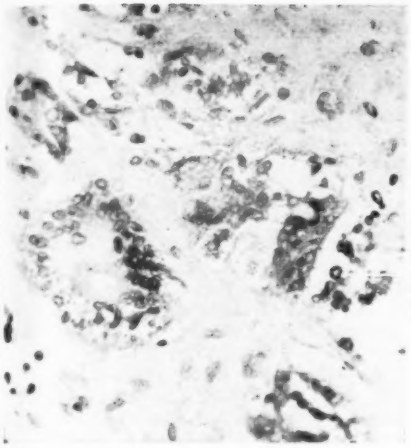



FIG. 1.—Torulosis of brain. Section showing proliferating *Cryptococcus neoformans* cells producing giant-cell reaction. (Stained periodic acid Schiff and haematoxylin. ×256.)

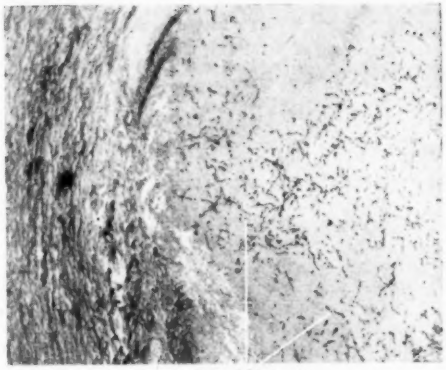



FIG. 2.—Aspergillosis of avian lung. *Aspergillus fumigatus* filaments in periphery of area of caseation. (Stained periodic acid Schiff. ×109.)

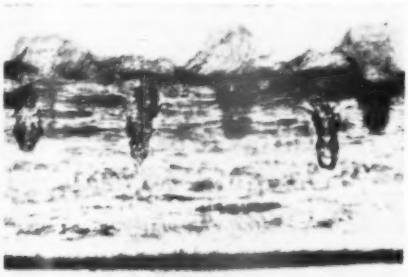


FIG. 3.—Penetration of hair keratin *in vitro* by *Trichophyton mentagrophytes*. (×107).

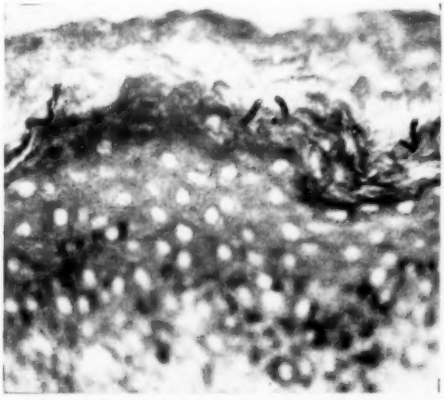


FIG. 4.—*Trichophyton rubrum* infection of dorsum of foot. Section showing fungus filaments deep in keratin near stratum granulosum. (Stained periodic acid Schiff. ×244.)

species to human disease processes. In Britain, where the more virulent types of pathogenic fungi are rarely met with, the role of the potential pathogen is of main importance.

I wish to acknowledge with thanks the help of Mr. R. J. Lunnon, Institute of Dermatology, for the photographs and of Miss Y. M. Clayton and Dr. C. D. Calnan for providing the material shown in Figs. 3 and 4 respectively.

## REFERENCES

DAWKINS, S. M., EDWARDS, J. M. B., and RIDDELL, R. Q. (1953) *Lancet*, ii, 1230.
HENRICI, A. T. (1939) *J. Immunol.*, **36**, 319.
PARTRIDGE, B. M. (1952) *Trans. St. John's Hosp. Derm. Soc., Lond.*, **31**, 34.
WINNER, H. I. (1956) *J. Path. Bact.*, **71**, 234.

# Observations on a Case of Torulosis associated with Hodgkin's Disease

By N. F. C. Gowing, M.D.

*London*

The various clinical, pathological and mycological aspects of human cryptococcosis (torulosis) have been well documented by a number of authors (Cox and Tolhurst, 1946; Baker and Haugen, 1955; Littman and Zimmerman, 1956) and the occurrence of disseminated cryptococcosis in Hodgkin's disease and other varieties of malignant lymphoma is now well recognized (Zimmerman and Rappaport, 1954; Zimmerman, 1955). Several reports have already appeared in the British literature (Levene and Michaels, 1955; Misch, 1955) but as such cases are relatively uncommon in this country it was thought that a further example might be of interest. The idea that these cases may represent a "Hodgkinoid" reaction to the cryptococci has now been generally discarded in favour of the concept of true Hodgkin's disease with secondary mycosis following depressed host resistance (Symmers, 1957); in this connexion the present case exhibits several interesting features.

## Clinical Summary

The patient, a man aged 36 years, was first seen at the Royal Marsden Hospital on August 20, 1956.

*Occupation.*—Machine assistant in glass factory.

*Previous medical history.*—Nothing of note.

*Family history.*—Three siblings alive and well. Father died of pneumonia at age of 56 years. Mother alive in mental hospital.

*Symptoms.*—Night sweats (at intervals) twenty-four months. Dysphagia twelve months. Increase in size of neck nine months. Non-productive cough six months. Fatigue six months.

*Clinical examination.*—Enlarged nodes in both supraclavicular fossæ, extending up both jugular chains. Small nodes palpable in axillæ. Spleen just palpable. Liver not enlarged.

*Investigations.*—X-ray chest: upper mediastinum broadened by enlarged lymph nodes on either side. Enlarged node in left hilum. Lung fields clear. Hæmoglobin 8·6 g./100 ml. P.C.V. 31%. M.C.H.C. 27·6%. The *red cells* showed slight anisocytosis and slight to moderate hypochromasia. White cell count 5,000 per c.mm. (polys. 57%, eosinos. 6%, basos. 1%, lymphos. 22%, monos. 14%). Platelets 305,000 per c.mm. (normal). Lymph node biopsy from right posterior cervical group (August 7, 1956): Hodgkin's disease.

*Treatment* (*August–September* 1956).—(1) Chemotherapy: Chlorambucil 12 mg. daily for fourteen days. (2) Radiotherapy to mediastinum (2,635 r) and neck (4,480 r).

*Course.*—Initial temporary improvement, but when seen in February 1957 his condition had deteriorated and he complained of extreme lassitude, dyspnœa, sweating and generalized pruritus.

*Further treatment* (*April–July* 1957).—Radiotherapy to mediastinum (2,500 r). Chlorambucil. Blood transfusion. Prednisolone. ACTH. Penicillin.

*Last admission to hospital* (*June* 18, 1957).—Patient moribund. Severe anæmia (Hb 46%). Œdema of both ankles. Extreme weakness. Liver and spleen both enlarged. Clinical evidence of peripheral circulatory failure. He died on July 3, 1957.

## Summary of Post-mortem Findings

*External.*—Body thin, but not emaciated. No skin lesions.

*Cardiovascular system.*—No significant changes.

*Respiratory system.*—There was pneumonic consolidation ("red hepatization") of the left lower lobe with fibrinous exudate on the overlying pleura. Mucopus was present in the bronchial tree.

*Alimentary system.*—The pharynx, œsophagus, stomach, intestines, pancreas and peritoneal membranes were normal. *The liver* (weight 2,400 grams) contained numerous small ill-defined greyish nodules of Hodgkin's tissue in both lobes.

*Genito-urinary system.*—No significant changes.

*Endocrine glands.*—The pituitary, thyroid and adrenals appeared normal. *The spleen* weighed 300 grams and contained greyish deposits of Hodgkin's tissue, producing the classical "hard-bake" appearance.

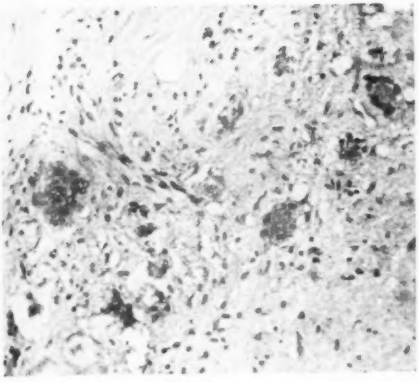


FIG. 1.

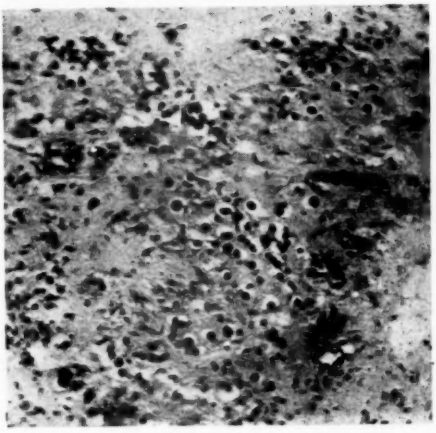


FIG. 2.

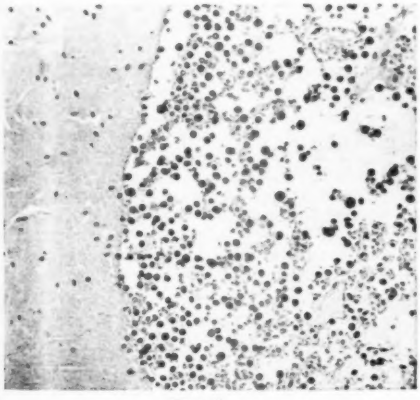


FIG. 3.

FIG. 1.—Mediastinal lymph node showing granulomatous reaction with giant cells of the "foreign body" or "Langhans" type. This contrasted with typical Hodgkin's tissue found in other sites. Hæmatoxylin and eosin. ×83.

FIG. 2.—Section from the same block as Fig. 1 stained to show the presence of numerous cryptococci. Hale's method for acid mucopolysaccharides. ×83.

FIG. 3.—Part of cerebellar cortex and adjacent leptomeninges showing numerous cryptococci in the subarachnoid space. Mucicarmine. ×83.

*Lymph nodes.*—There was moderate enlargement of the nodes in the axillæ, neck, mediastinum and abdomen (chiefly para-aortic). The nodes were firm in consistency and greyish in colour with yellowish flecks of necrosis; the largest glands were about 3 cm. in diameter.

*Central nervous system.*—There was some opacity in the leptomeninges, especially over the base of the brain, but the significance of this was considered uncertain on macroscopic examination.

## HISTOLOGY

Torulosis was not suspected during life and culture of the organism was not obtained. However, the morphology and staining properties of the fungus were typical (Kade and Kaplan, 1955). The following points are of particular interest: (1) No cryptococci could be found in the original lymph node biopsy, even after prolonged search of many sections. (2) Tiny necrotic foci containing cryptococci were present in the lungs and there were granulomatous lesions with numerous organisms in some of the mediastinal lymph nodes. (The lobar pneumonia was apparently a separate terminal event.) (3) No cryptococci could be found in the extensive deposits of Hodgkin's disease in the abdominal lymph nodes, spleen and liver. (4) The tissue reaction to the cryptococci was histologically dissimilar to Hodgkin's disease and showed features akin to other types of infective granuloma (Figs. 1 and 2). (5) There was a severe cryptococcal meningitis (Fig. 3) but the tissue reaction at this site was much less marked than in the mediastinal lymph nodes. A few groups of organisms were found within the cerebral and cerebellar cortices.

The pathological findings and the distribution of the cryptococci in this case do not support the idea of a "Hodgkinoid" reaction to a primary fungal infection but suggest the following sequence of events: (1) Hodgkin's disease, (2) Infection with cryptococci through the respiratory tract with the development of cryptococcal granulomas in the lungs and mediastinal lymph nodes, (3) Terminal dissemination of cryptococci to the central nervous system through the blood stream.

ACKNOWLEDGMENTS

I would like to thank Mr. R. C. B. Ledlie, F.R.C.S., for permission to use the clinical notes. Mr. Kenneth Moreman of the Chester Beatty Research Institute prepared the photomicrographs.

REFERENCES

BAKER, R. D., and HAUGEN, R. K. (1955) *Amer. J. clin. Path.*, **25**, 14.
COX, L. B., and TOLHURST, J. C. (1946) Human Torulosis. Melbourne.
KADE, H., and KAPLAN, L. (1955) *Arch. Path.*, **59**, 571.
LEVENE, M., and MICHAELS, L. (1955) *J. clin. Path.*, **8**, 201.
LITTMANN, M. L., and ZIMMERMAN, L. E. (1956) Cryptococcosis—Torulosis, or European Blastomycosis. New York and London.
MISCH, K. A. (1955) *J. clin. Path.*, **8**, 207.
SYMMERS, W. ST. C. (1957) *Brit. med. J.*, ii, 459.
ZIMMERMAN, L. E. (1955) *Amer. J. clin. Path.*, **25**, 46.
—— , and RAPPAPORT, H. (1954) *Amer. J. clin. Path.*, **24**, 1050.

# An Experimental Approach to the Study of Infections by Yeast-like Organisms

By H. I. WINNER, M.D.
*London*

FEW unexplored subcontinents remain to the worker in experimental infections; one such is mycology. Because the experimental pathology of fungous infections has not been fully investigated, there is a tendency in clinical mycology to borrow ready-made concepts from bacterial infection. For example, cases of systemic moniliasis have been treated with anti-monilial rabbit serum, on the assumption that the possession of such antibodies would benefit the patient. Attempts have been made to produce active immunization against blastomycosis with killed vaccines, on the same assumption. This is in spite of the fact that these classical immunological concepts cannot be applied to the more complicated bacteria; one does not try to immunize against the tubercle bacillus or *Treponema pallidum* by such means, and one would expect that immunity mechanisms in mycoses would be more akin to those operating in tuberculosis than to those operating in typhoid.

There are several *a priori* reasons why one should be cautious about applying the well-tried immunity concepts of bacterial and virus infection to fungal infection without verifying them experimentally. The first and most obvious is the much larger size of the infecting organism. When considering bacterial and virus infection, it can be assumed that the infecting agent is smaller than the smallest host cells, and that it can pass between cells, across capillary walls, and across cellular membranes such as the glomerular basement membrane without causing any mechanical disturbance. In the case of the fungi these things cannot be assumed. The pathogenic yeasts have approximately the diameter of a red blood cell, and a mean volume which is slightly greater. Their very presence in the host, even considered as inert particles, raises mechanical problems by virtue of their size alone. Further, many of these organisms, such as *Candida albicans*, produce mycelium, and a rapidly growing proliferating yeast is a large object inside the host tissues (Fig. 1).

Secondly, one would expect the tough polysaccharide wall of yeast cells to protect them from damage by the aggressive mechanisms of the host. The yeasts are likely to be relatively immune to the digestive action of the host enzymes, to surface-acting antibodies, to such agents as lysozyme, and to phagocytosis.

Thirdly, because of their more complex organization, one would expect fungi to have more complex enzyme systems than bacteria. The existence of these systems, operating within a metazoan host, would raise problems for both host and invader. Again, the large fungal cell must possess very many antigens. When one considers that a salmonella, with a volume of about 1 cubic micron, contains a battery of several flagellar antigens and another battery or batteries of somatic antigens, one would expect a yeast cell, with a volume

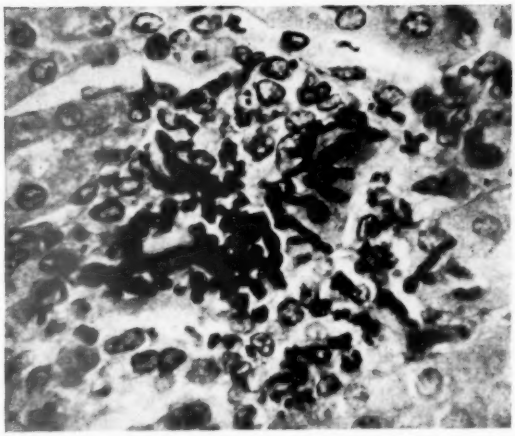


FIG. 1.—Yeast proliferating in tubule of rabbit kidney, twenty-four hours after infection with *Candida albicans*. Note absence of inflammatory response. PAS—hæmatoxylin. ×470.

of about 130 cubic microns, to be very much more complex antigenically. In fact, one would expect the pathogenic yeasts to possess a variety of antigenic mechanisms, not one of which is at present as well defined as are, for example, the exotoxins of *Streptococcus pyogenes*. It is relevant also that skin hypersensitivity reactions to whole fungus or to extracts can often be demonstrated in fungous infection, though their significance is not understood and their occurrence is not constant.

In the present reconnaissance of the field, I am concerned largely with the problem of why some yeasts are pathogenic and others are not, and why some are more pathogenic in particular circumstances than in others.

*Candida albicans*, for example, is often found on the skin as a commensal. It is only rarely found there as a pathogen, mostly in cases of intertrigo or paronychia. Various influences have been postulated to bring about the change from commensal to pathogen, such as antibiotic therapy, agranulocytosis, cortisone therapy. Maceration is a possible cause. Experimentally, it is difficult to implant the organism into the skin of a guinea-pig by any means short of intradermal injection. I have tried various methods and failed; for example, maceration with waterproof dressings, painting the organism on to the intact or the damaged skin, or firing it into intact or injured skin with a Heaf gun.

Intradermal injection of the living organisms into guinea-pigs and rabbits causes a self-limiting disease. An inflammatory nodule forms with central necrosis; the organism is extruded with some pus and necrotic cells, leaving a clean ulcer which gradually heals. A similar but smaller lesion is produced by formalin-killed and washed organisms, and similar lesions are produced by related species of yeasts, both living and formalin-killed. Strangely enough, killed *Cryptococcus neoformans* is less toxic to the skin than killed yeasts of the genus *Candida*.

Systemic cortisone does not have an adverse effect on the development of the intradermal lesion. In fact, the size and duration of the lesions in cortisone-treated animals are, if anything, rather less than in the untreated.

TABLE I.—THE DIAMETER OF 3-DAY LESIONS IN GUINEA-PIGS FOLLOWING INTRADERMAL INJECTION OF *Candida albicans*

(in centimetres)

| | Cortisone-treated animals | Untreated animals |
|---|---|---|
| | 1·2 | 1·4 |
| | 0·7 | 1·4 |
| | 1·3 | 1·5 |
| | 1·0 | 1·4 |
| | 1·2 | 1·5 |
| | 0·9 | 1·5 |
| mean: | 1·05 | 1·45 |

If living organisms of the candida group are injected into the peritoneal cavity, again they do not cause a progressive disease, nor does cortisone treatment affect them adversely. After intraperitoneal injection of *Candida albicans*, guinea-pigs show a peritonitis in a week or so. One may find one or two abscesses on the liver, but the organisms do not invade. If the animals are left a few weeks before sacrifice, no evidence of disease is found. Other yeasts of this group cause a less marked, more transient peritoneal reaction.

The most interesting features are seen in blood stream infections. If various yeasts of the candida group are injected intravenously into rabbits in large doses, only *C. albicans* produces disease, the other yeasts do not. And the systemic disease so produced is fatal within a few days, in both rabbits and guinea-pigs.

The histological features of this disease have been described elsewhere (Evans and Winner, 1954). I want to draw attention to one or two of the more striking points.

First, one is struck at necropsy by the apparent lack of involvement of the lymphoreticular system. Although the animals have died of a blood-stream infection, neither spleen nor lymph nodes are enlarged or septic. Secondly, the lesions show a large amount of yeast, but a small amount of cellular reaction (Fig. 1). These two features are in sharp contrast to what is seen in most bacterial or viral infections, and they suggest that the immunity mechanisms of the host are not adapted to dealing with this type of infection.

In the systemic disease in rabbits, the most prominent lesions are to be seen in the kidneys (Evans and Winner, 1954). The clinical picture is one of gradually increasing listlessness and inactivity, oliguria, sometimes coma or convulsions, and at death the animals have a high blood urea. The immediate cause of death is uræmia.

It is tempting to suggest that the uræmia is due to the mechanical presence of this large organism in the kidney, causing the renal function to diminish until it can no longer support life. Further experiments show that this is too simple a view. If animals are actively immunized by repeated injections of the living organism, they are not thereby protected from the lethal effects of the organism (Winner, 1956). Immunization, using the word in its specialized sense, does not protect the animals at all, nor does the possession of natural agglutinins.

One must remember that antibodies induced by this type of whole-cell immunization are surface-acting antibodies. Unless the lethal mechanisms of the yeast lie on the surface of the cell, and there is no reason to suppose that they do, one would not expect them to be affected by these antibodies.

Another feature of the disease is revealed by injecting graded doses of the organism into rabbits. There is a definite threshold dose, below which the animal recovers from a transient illness, but above which it dies. Of 43 animals which received 5 million organisms or more, only one survived. On the other hand, 24 animals which received less than 2 million organisms all survived. Thus the natural defences of the animal are not entirely impotent (Winner, 1956).

This experimental disease, then, shows a number of unusual features which are probably related. They are as follows:

(1) Lack of involvement of the spleen and lymph nodes.

(2) Relatively poor cellular response seen in histological sections.

(3) Failure of agglutinating antibodies to protect against the lethal effects of the organism.

(4) Well-defined threshold dose of organism necessary to produce death.

A fifth characteristic, about which at the moment I feel rather diffident, is

(5) Failure of systemic cortisone to enhance the disease.

The first three at least of these characteristics are points of difference between systemic moniliasis and most types of bacterial and virus infection. Considered with the histological picture, they suggest that mechanical factors play a large part in the pathogenesis of the disease, but that they are not the whole story. The mechanical action of yeast cells will not of itself cause death. One may inject massive doses of killed *C. albicans* into rabbits, and the animals are none the worse; not only do they not become ill, but it is extremely difficult to detect the organisms later. Large doses of living cultures of other, antigenically related, organisms, such as *Candida tropicalis*, *C. pseudotropicalis*, *C. guilliermondi*, *C. stellatoidea*, and *C. parakrusei*, do not cause death or any detectable illness in the animals after intravenous injection. These species are evidently unable to multiply in the rabbit tissues, whereas *C. albicans* possesses some specific factor enabling it to establish itself, thereby producing disease.

I have mentioned the relatively poor cellular response which is found in the lesions in experimental moniliasis. This is not invariable; occasionally a different kind of lesion with much cellular necrosis and a well-marked inflammatory exudate is seen, suggesting either that some diffusible toxin is at work or that a hypersensitivity reaction is taking place.

Henrici (1940) postulated that *C. albicans* produces an exotoxin. If this were true, it would explain many features of the experimental disease. Now, if *C. albicans* is grown in peptone water at 37° C. for a few days, some of the culture filtrates will produce erythema in guinea-pigs and rabbits. Heated filtrates produce the same effect, which is not seen in cortisone-treated animals. Attempts to isolate this toxic factor have not as yet succeeded. At the moment I am trying to find out whether similar factors are to be found in filtrates of other species of candida. If not, this may be part of the answer to the question of why *C. albicans* is pathogenic on intravenous injection but the other yeasts are not. Yet it is not the whole answer. The filtrates themselves produce no detectable ill-effect when injected intravenously into rabbits. If formalin-killed *C. albicans* is suspended in culture filtrate, and injected intravenously, no ill-effects are produced. Similarly, if living cultures of the non-pathogenic yeasts are washed, suspended in *C. albicans* filtrate, and injected intravenously, they remain non-pathogenic.

However, these experiments are still in the early stages.

This work is assisted by a grant from the Clinical Research Subcommittee of Charing Cross Hospital.

REFERENCES

EVANS, W. E. D., and WINNER, H. I. (1954) *J. Path. Bact.*, **67**, 531.
HENRICI, A. T. (1940) *J. Bact.*, **39**, 113.
WINNER, H. I. (1956) *J. Path. Bact.*, **71**, 234.

## Multiple Fungous Infections of Skin

By BETTY M. PARTRIDGE, M.A.
*London*

THIS study deals with those multiple infections due to fungi which were encountered among the last 5,500 patients examined at the Institute of Dermatology. These had been referred to the Department of Medical Mycology after a report was received from the routine laboratory that fungus was present on direct examination of keratinous tissues. On 52 occasions two dermatophytes, or ringworm fungi, were isolated from the same patient, and in a further 27 instances a dermatophyte and some other fungus, such as *Malassezia furfur*, *Nocardia minutissima* or *Candida albicans*, were recovered.

In a brief survey of these cases, reference will be made to the occurrence of *Trichophyton rubrum*. In almost all the patients with a double dermatophyte infection, the clinical picture simulated that associated with *Trichophyton rubrum* infections, and this organism was isolated from over 80% of these cases. Other ringworm organisms tend to produce rather characteristic clinical pictures of their own, generally distinguishable from what one might call the "*Trichophyton rubrum* syndrome". Briefly, this has an insidious onset, usually beginning with foot lesions and with later spread to the hands in nearly 50% of cases. Nail involvement is frequent, the nails becoming thickened, discoloured and friable. With spread to the crural region, the thighs and buttocks become involved rather than the groin. Careful laboratory examination is often necessary to detect the presence of fungus.

Multiple fungous infections will be referred to either as combined or concurrent infections. A combined infection means that more than one fungus was cultured from the same lesion. A concurrent infection means that more than one fungus was grown from separate lesions on the same occasion. Combined and concurrent infections may occur simultaneously.

The first group of multiple dermatophyte infections includes those in which *Trichophyton interdigitale* occurred with *Trichophyton rubrum*. These two dermatophytes were isolated from 20 patients in all. In 8 both organisms were cultured from the same lesion, i.e. there was a combined infection; in the other 12, the infections were concurrent. *Trichophyton interdigitale* was isolated from the feet in all 20, although all but one patient appeared clinically to be infected by *Trichophyton rubrum*. In nearly all the patients, the disease had been present for several years.

*Epidermophyton floccosum* and *Trichophyton rubrum* were found together on 17 occasions, 6 times as concurrent infections, and 11 times as combined infections. As with *T. interdigitale* in the first group, *E. floccosum* was grown from the feet, usually from toe webs, of all but 2 of these patients. Clinical evidence of infection with *E. floccosum* was apparent in only 8 of the patients, either as interdigital maceration, or as symmetrical, scaly, erythematous eruptions of the groin. With one exception, all the patients in this group were suffering from chronic

*T. rubrum* infections of the feet; many had nail involvement, and the disease had spread to the hands in all but 3 of them.

We must next consider the association of *Epidermophyton floccosum* and *Trichophyton interdigitale*. There were 6 cases of this kind in which *Trichophyton rubrum* was absent. As in the first group, *T. interdigitale* was isolated only from the feet on each occasion. 3 of the patients showed clinical evidence, subsequently confirmed by culture, of an *E. floccosum* or *T. interdigitale* infection of the feet. The other 3 presented with what appeared to be a typical persistent *T. rubrum* infection of the hand, although only *E. floccosum* was grown in each instance.

Other dermatophytes isolated with *T. rubrum* include *Trichophyton violaceum*, *T. tonsurans* and *T. sulphureum*, and *Microsporum canis* and *M. gypseum*.

*Trichophyton violaceum* was isolated from the buttocks of a patient who had an infection involving the feet and hands, buttocks, neck and ears. *T. rubrum* was thought to be the causative organism and was in fact cultured from the feet.

*Trichophyton tonsurans* has also been grown together with *T. rubrum* from the buttocks of a patient suffering from a mild, non-erythematous scaling of many parts of the body.

An interesting concurrent infection from which *Trichophyton sulphureum* and *Trichophyton interdigitale* were isolated, was seen in a patient whose palm and finger-nail disease appeared clinically to be caused by *T. rubrum*. *T. sulphureum* was repeatedly cultured from the index finger and nail, and *T. interdigitale* from mild interdigital scaling of the feet.

A *Microsporum* species has surprisingly enough been found on 6 occasions in multiple infections. In each case it was grown from the feet with either *T. rubrum* or *T. interdigitale*.

It is not unexpected that fungi causing the more superficial infections, such as pityriasis versicolor and erythrasma, occur simultaneously with ringworm infections. This was recorded in 9 patients. In 7 of these the dermatophyte was *T. rubrum*. The onset and duration of both types of infection appeared to run a parallel course. Such multiple fungous infections may indicate a predisposition of some patients to fungous infection in general.

The significance of *Candida albicans* is frequently controversial, but to complete this account it should be stated that *Candida albicans* and a dermatophyte were isolated from 21 patients. In all but one instance, the dermatophyte was either *Trichophyton rubrum* or *T. interdigitale*.

## Discussion

A summary of the cases mentioned will show that *Trichophyton rubrum* was the most frequent organism recovered from the 79 multiple fungous infections reported. It was isolated on 57 occasions, 42 times with another dermatophyte, and 15 times with some other fungus.

In the multiple dermatophyte infections where *T. rubrum* was one of the pathogens, the clinical picture usually conformed with that associated with single infections by this organism. When *T. interdigitale* was the second pathogen it was always isolated from the feet, and only once was its presence clinically suspected in concurrent infections with *T. rubrum*. *Trichophyton interdigitale* alone, only rarely produced an infection resembling that of *T. rubrum*.

On each of the 17 occasions that *E. floccosum* was present in a multiple infection, it was isolated from intertriginous areas. Clinically, its presence was suspected in 10 patients, but extension of the infection from such areas produced a picture similar to that associated with *T. rubrum*. That an infection by *E. floccosum* can simulate the "*T. rubrum* syndrome" is borne out by the number of instances (over 40) encountered during our routine mycological examinations, where *E. floccosum* alone was isolated in culture. Either these infections are multiple dermatophyte infections in which *T. rubrum* could not be isolated, or *E. floccosum* not uncommonly behaves like *T. rubrum*.

The primary causative organism in multiple infections can rarely be ascertained. The frequency with which *T. rubrum* was isolated is probably a reflection of the chronicity of the ringworm it produces, rather than of any significant relationship between it and other dermatophytes. Patients infected by *T. rubrum* may well acquire infection by some other organisms during the course of their disease. Furthermore, owing to the chronicity of *T. rubrum* infections, such patients will tend to receive more careful and repetitive examination. Even so, it is felt that this does not fully explain the high proportion of *T. rubrum* isolations recorded in multiple infections. Patients who become infected with this organism may be a group susceptible to any fungous infection.

In conclusion it should be stressed that the total number of multiple infections recorded is less than 1·5% of the total number of fungous infections confirmed by culture in our department. Of the multiple dermatophyte infections, the number in which *T. rubrum* was present is less than 4% of the total number of patients from whom this organism has been isolated.

# The Occurrence of *Aspergillus fumigatus* in Respiratory Infections

By YVONNE M. CLAYTON, B.Sc.
*London*

DURING the past year, observations have been made on the fungi isolated from routine sputa cultured on Sabouraud's dextrose agar at both 22° C. and 37° C. Because of the ubiquity of fungus spores in the atmosphere it is not unexpected that filamentous fungi are isolated in sputum cultures quite often; yeasts, part of the commensal flora, are present with greater frequency. Sputa from 1,700 consecutive patients suffering from various diseases were examined by culture at 37° C., and, as was to be expected, 43% of them harboured *Candida albicans*. Of several other yeasts which were grown, *C. tropicalis* and *Torulopsis glabrata* were the most frequent to be isolated, each occurring in about 5% of patients. *Aspergillus fumigatus* was isolated from about 6% of these patients; it colonizes readily within bronchi and damaged lung tissues and has pathogenic properties not possessed by other contaminating fungi. Other filamentous fungi, including, *A. niger*, *A. nidulans*, *Penicillium* sp., *Paecilomyces*, *Mucor* sp., &c., were in all isolated from only 3% of this group. When sputum was cultured at room temperature, *A. fumigatus* was less predominant; *Penicillium* species were isolated and recorded with much greater frequency, as were other contaminants like *Paecilomyces* species. In a recent series of sputa cultured for one week, 142 specimens yielded *Penicillium* species at 22° C., compared with only 18 isolations from the same specimens at 37° C. The reverse occurred in the case of *A. fumigatus*. This fungus was grown from 25 specimens at 22° C. compared with 69 specimens at 37° C. Therefore for an examination of sputum specimens, an adequate primary isolation of fungi can only be achieved if both temperatures are used in the cultural studies.

It is hoped from studies of this kind to establish the relative importance of these contaminating fungi, and of *A. fumigatus* in particular, in one of four different possible roles. Firstly, the fungi may be transient residents in the bronchi following inhalation. Secondly, they may be persistent or recurrent allergens in the respiratory tract of asthmatic patients. Thirdly, they may be persistent or recurrent residents in the so-called allergic type of aspergillosis so fully described by Hinson *et al.* (1952), a condition which appears to be quite distinct from asthma. And, lastly, the source of the fungus may be from a focus of infection in damaged lung, as for example, from an infected cavity, or from a mycetoma.

We have at the moment no conclusions to report about the ability of fungus spores to persist in the respiratory tract of normal or diseased subjects. The second possibility, that *A. fumigatus* may be a responsible allergen in asthma patients, is at present receiving further study.

In the allergic type of aspergillosis, the fungus apparently excites the secretion of exudate which temporarily obstructs the bronchial lumen, giving rise to collapse of affected portions of the lungs. In our experience, only *A. fumigatus* is associated with this syndrome. A notable feature is the scantiness of the fungus in the bronchial secretions; the tenacious exudate expectorated by these patients during an attack has often to be examined with great care in order to demonstrate the fungus filaments within it. On receipt of a clinical history typical of this kind of infection, repeated examinations of sputa should be made if no fungus is isolated in the first attempts. The form of the fungus in the bronchial exudates of the hypersensitive group of patients is mycelial whereas spores are presumably responsible for attacks in asthma patients. The well-recognized predisposition to this disease which occurs in agricultural workers, gardeners, poultry keepers and others handling hay, straw, or cereals on which *A. fumigatus* readily vegetates, has been obvious in our series of patients. The presence of the fungus in the sputum of this particular type of subject is, however, clearly a matter for very careful interpretation.

Finally, the fourth possible role of these fungi, namely as invaders of lung tissue or of tissue spaces: In our experience, such invasion always occurs in lungs previously damaged in some way and *A. fumigatus* alone has been responsible. The abundance of fungus growth in the pulmonary tissues is a notable feature of these cases. The readiness or difficulty with which the fungus is isolated from the sputum will depend quite obviously on the freedom of communication of the diseased area with the bronchial tree. Where the walls of a cavity are invaded and air is present to allow sporulation, then sporing structures may appear in the sputum. On the other hand, in those cases where the fungus is vegetating in a closed space the structural form of the fungus is mycelial and it is very rare to find sporing structures present. The lobulated mass of a mycetoma consists almost entirely of fungus mycelium and abortive attempts at sporulation on the surface can only be found with difficulty. Sectioning of these mycetomata has shown that the superficial parts of the fungus mass

consist of actively growing healthy fungus mycelium from which positive cultures may readily be obtained. As one gets towards the centre of the mass there is, however, a predominance of degenerate mycelium and cultures from this zone are often sterile. It would seem that a feature of at least some of these mycetomata is to produce white non-sporing cultures on Sabouraud's medium on primary isolation (Riddell and Clayton, 1958). After prolonged culture scanty patches of greenish areas typical of *A. fumigatus* may develop which allow identification to be made. Therefore, when the presence of a mycetoma is suspected great care and sufficient time should be taken to identify completely any white non-sporing fungus isolated from the sputum or resected lung.

## REFERENCES

HINSON, K. F. W., MOON, A. J., and PLUMMER, N. S. (1952) *Thorax*, **7**, 317.
RIDDELL, R. W., and CLAYTON, Y. M. (1958) *Brit. J. Tuberc.*, **52**, 34.

## DISCUSSION

**Mr. P. K. C. Austwick** wondered whether a few comments from the point of view of animal mycoses might not be useful.

Dr. Riddell had given a very interesting survey of the pathogenic role of fungi and Mr. Austwick understood that he concluded that many of the fungi causing systemic mycoses were essentially saprophytic in the body. This concept may possibly be disputed on the grounds that a species such as *Aspergillus fumigatus* can be demonstrated to be primarily pathogenic and moreover usually has a distinct parasitic morphology in the infected tissue.

Dr. Winner's paper was a notable and fascinating contribution to the study of pathogenic yeasts and would provide much stimulation for those engaged in accumulating knowledge of this type of infection in animals. He also indicated a way in which some of the fundamental problems of fungal pathogenicity may be approached.

Apart from their mycological interest, the importance of the dual ringworm infections described by Miss Partridge appeared to lie in the trouble which they might cause when specific methods of therapy are available.

Miss Clayton had ably demonstrated the necessity of using a second, lower temperature of incubation when dealing with certain morbid materials in order to obtain a more complete picture of the presence of fungi. Such apparently saprophytic fungi isolated in this way may have a pathogenic significance at present unsuspected.

**Dr. A. W. Frankland,** in answer to a question about susceptibility of birds to aspergillosis, said that J. V. Beer at the Wildfowl Trust, Slimbridge, had found that it was possible to culture *Aspergillus fumigatus* from the throats of 10% of the healthy birds.

Dr. Elizabeth Hamilton working at the Wright-Fleming Institute had always been able to find aspergilli in the bird seed fed to budgerigars. He believed that this source is the commonest potential hazard in patients with pulmonary eosinophilia due to aspergillus sensititivity.

The bacteriological findings in sputum specimens may represent contaminants from the throat. He asked Dr. Riddell if, when *Aspergillus fumigatus* was grown from a sputum culture, he considered that the spores had necessarily reached the bronchial tree? Also using careful mycological technique, how often would it be possible to culture aspergilli from the sputum of a chronic bronchitic?

**Dr. J. Pepys** said that, in view of the importance of allergic sensitivity to the airborne spores of fungi in asthma, it would be helpful to know in the case of *Aspergillus fumigatus*, for example, where the fungus is commonly encountered in appreciable amounts, and whether its incidence is affected by climatic, seasonal and geographical variations.

**Mr. Austwick,** in reply to Dr. Pepys' question about the natural occurrence of *Aspergillus fumigatus*, said that it was present in small quantities almost everywhere in soil, but only developed profusely in decomposing plant and animal products, for instance in hay and straw, more especially when these had been allowed to heat up during storage.

**Dr. Riddell** agreed with Dr. Frankland that *Aspergillus fumigatus* might be a throat contaminant. He could not say in what proportion of those patients growing *A. fumigatus* from their sputum the fungus had originated from the bronchial tree. Bronchial aspirates examined from a few patients had shown that this was the case in at least a small proportion.

*Aspergillus fumigatus* had been present in the sputum of approximately 5% of 600 bronchitics examined at the Brompton Hospital.

# Section of Surgery

President—A. DICKSON WRIGHT, M.S., F.R.C.S.

[*January* 8, 1958]

MEETING HELD AT ST. MARY'S HOSPITAL, LONDON

THE programme included operations, demonstrations and short papers, as follows:

OPERATIONS

**Resection of Abdominal Aneurysm.**—Professor C. G. ROB.
**Abdomino-thoracic Nephrectomy for Renal Tumour.**—Mr. H. H. G. EASTCOTT.
**Exploration of the Common Bile Duct.**—Mr. A. DICKSON WRIGHT.
**Partial Gastrectomy.**—Sir ARTHUR PORRITT.

SHORT PAPERS

**On Some Surgical Aspects of Thyroid Disease.**—Mr. H. H. G. EASTCOTT.
**Surgical Treatment of Carotid Arterial Occlusion.**—Professor C. G. ROB.
**Conservative Treatment of Carcinoma of the Breast.**—Sir ARTHUR PORRITT.

DEMONSTRATIONS

**Citrate Intoxication.**—Mr. JOHN LUDBROOK.
**Treatment of Intermittent Claudication by Amnion Implant.**—Mr. H. H. G. EASTCOTT and Dr. M. J. O. MASSEY.

Cases were also demonstrated.

[*February* 5, 1958]

## DISCUSSION ON SMALL BOWEL OBSTRUCTION [*Abridged*]

**Mr. Robert V. Cooke** (Bristol):

"*Diseases of stoppings and suffocations are the most dangerous in the body.*"—BACON.

The first question I wish to raise is whether advances in our understanding of the biochemical effects of small bowel obstruction and in anæsthesia have been paralleled by similar advances in diagnosis and treatment. I would contend that they have not, and I suspect that it is for this reason we have been asked to take stock of our position. Fig. 1, based on the

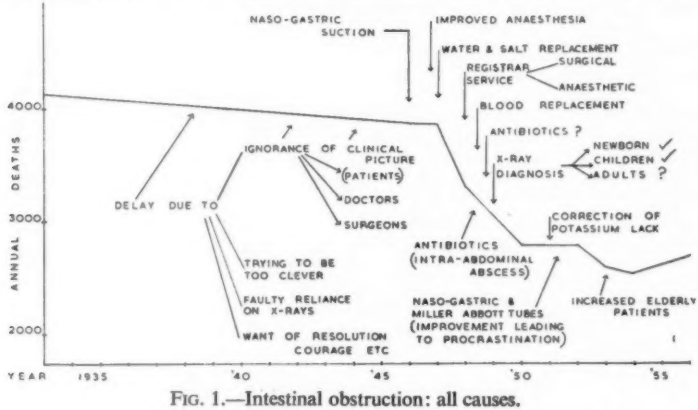



FIG. 1.—Intestinal obstruction: all causes.

Registrar-General's Reports, indicates what has been happening since Mr. Vick's monumental survey. Some of the factors operating during this period have been indicated.[1]

The initial post-war improvement, so largely due to our registrars, has been followed by an unsatisfactory lull.

Most of us with extensive clinical experience would admit with sorrow that we can remember tragic deaths resulting from want of timely surgical intervention. My own experiences together with what I have heard up and down the country have but strengthened my anxiety of

(1) the practice of trying to distinguish between simple and strangulated obstruction, basing treatment on that distinction;
(2) the use of the Miller-Abbott tube, in *acute* obstruction of the small intestine;
(3) endless suction and infusion—instead of expeditious surgery.

Surely we would agree with Sir Heneage Ogilvie that "in the acute abdominal emergencies the difference between the best and the worst surgery is infinitely less than that between early and late surgery, and the greatest sacrifice of all is the sacrifice of time".

The first line of defence is the general practitioner and we must remember that we are responsible for his training. We must also remember that on an average the doctor in practice sees only two acute obstructions a year. Nevertheless, as Rutherford Morrison used to put it: "The fate of a patient, the victim of an abdominal emergency, depends chiefly upon the skill and promptitude of his doctor." Surgeons, too, are not infrequently guilty of diagnostic errors and delays in dealing with intestinal obstruction. We must face facts and admit that disasters from intestinal obstruction are still too frequent. We ourselves may be alive to them, but we have not been teaching their lessons forcefully or frequently enough to others.

In our larger hospitals, most of this difficult work is shouldered by our senior registrars. In response to our request surgical colleagues and their registrars have given us a wealth of material and figures from which I can only extract some of the more essential points.

The questions put to them were:

(1) Do they find themselves able at all readily to distinguish between simple and strangulated obstructions? If they feel they can, how often have they found themselves to be wrong, and with what results? Do they go to great lengths to correct water and salt depletion before operation? Are they satisfied that whole blood has a place in treatment?
(2) Have they come to the conclusion that, acute obstruction being diagnosed, the earliest possible operation is indicated in almost every case, the exact state of affairs being unpredictable? (Obviously a short time must be given to fluid and blood replacement in those later cases with severe dehydration or shock.)
(3) What type or types of case provide them with most anxieties? I was particularly interested in post-operative obstructions, how they deal with them, and the results. Any convictions firmly held would be most valuable.

Nearly all senior registrars felt unable with any certainty to distinguish between simple acute obstruction and strangulated obstruction. Some "considered it useless to try since both conditions are deadly dangerous, and the earliest operative relief is essential". Some took the view that it was "a good academic exercise" in clinical diagnosis but highly dangerous if the exercise delayed surgical relief. A few felt fairly confident of making the distinction, but all admitted mistakes.

Nearly everyone felt that the average case, seen reasonably early before there was clinical evidence of fluid depletion, should be operated on at once. Many had learned by experience the value of whole blood when there was clinical shock, even if the blood pressure had not actually fallen to shock level. Much blood is lost to the circulating blood volume when any considerable length of bowel is strangulated or infarcted, both in its walls and in its lumen.

Some consultants as well as registrars were sceptical of laboratory estimations, since there was a wide latitude of safety and some dehydration was less harmful than over-hydration. They thought clinical appraisement was sufficient. The case coming in late with gross dehydration and perhaps evidence of peripheral vascular failure was a special problem. We would all give a few hours, and many stipulated one to two hours, to try to bring such a patient into a better condition for operation, using large quantities of fluid, some salt, and one or two pints of whole blood if available. One has seen such cases deteriorating in spite of these efforts, and many of the registrars made this same observation. Under general anæsthesia, provided a high oxygen concentration is used, these cases often improve "in quite a striking fashion". With a massive volvulus untwisted and with plenty of oxygen there is often immediate and striking improvement.

Everyone agreed that it was proper to delay with the less acute case with slower onset in which there had been previous operations for diffuse adhesions with obstruction. Even in these cases, delay with suction and drip could be overdone. If surgery was performed, there was considerable difference of opinion about the best procedure. With the more acute episode over, there is time to carry out radiological investigation of the small intestine. A loaded-tip tube can be negotiated into the duodenum and small intestine. Barium can be instilled and used to show up a point of narrowed lumen. A planned operation may be deemed advisable,—perhaps on the lines of the Noble procedure.

*Operative Decompression*

The value of this procedure is emphasized by some but not mentioned by most. For many years it has been my practice to empty very distended coils by a long wide-bore needle and suction, closing the tiny holes with a single stitch. A similar practice is followed by some, and special suction-trocars have been devised. With most of the distension relieved, the recovery of the bowel is hastened, corrective surgery is facilitated, and so is the closure of the abdomen. Perhaps equally or more important is the removal of the pent-up fluid which may be toxic or contain substances which lower the blood pressure even to lethal levels once it is released and absorbed from the distal healthy reaches of the intestine.

Whatever the precise cause for this well-attested phenomenon it does seem that it may be worth while to have recourse to operative decompression much more than is the case, though some of the results made available were so good without such practice that it would be difficult to press this point too far.

Many take the view that the cause of the rapid deterioration following relief is solely due to fluid loss. Mr. Judson Chesterman writes to say:

"I do not think Registrars appreciate the fact that if you release loops of bowel of four or five feet in length, which are strangulated but viable, the patient will die very rapidly from fluid loss into the wall and lumen of the area involved unless fluid replacement is carried on immediately and in large quantities. Deaths from this are often attributed to anæsthesia and other conditions. I think it has been shown quite conclusively in cats that the animal dies more quickly with release of such a strangulation if the fluid balance is not immediately attended to, than it would have done if the strangulation was left to take its normal course to peritonitis and death.

To reiterate, though we like to think we can make an intelligent guess at the precise condition of affairs within the abdomen, we delude ourselves if we think we can be so sure as deliberately to withhold surgery and rely on suction decompression and intravenous medication instead. I contend that if you make a list of all the so-called distinguishing signs of strangulation: severity of onset; presence of shock; continuous, as well as colicky pain; fever; tachycardia; raised white cell count; distension or its absence; tenderness and rebound tenderness; palpable mass *per anum*, *vaginum* or *rectum;* all these, together with X-rays and auscultation too, can mislead. The diagnosis is primarily a clinical one. X-rays, if they are of first-class quality and expertly interpreted, may serve to support a diagnosis, occasionally help to refute it, and are rarely the sole means of making it. It is almost more important to be aware of its limitations than its value, though in neo-natal obstruction it is of great value. Tables I and II give an analysis of the cases of small bowel intestinal obstruction admitted to

TABLE I.—SMALL BOWEL OBSTRUCTION.
BRISTOL TEACHING HOSPITAL, 1952–1957

| | Cases | Deaths | % |
|---|---|---|---|
| Ing. hernia .. .. .. | 92 | 10 | 11 |
| Fem. „ .. .. .. | 102 | 6 | 6 |
| Vent. „ .. .. .. | 26 | 7 | 27 |
| Odd. „ .. .. .. | 4 | 0 | 0 |
| Adhesions .. .. .. | 39 | 8 | 20 |
| Lumen obstr. .. .. .. | 26 | 4 | 15 |
| Bands with strang. .. .. | 39 | 2 | 5 |
| Strang. obstr. .. .. | 16 | 0 | 0 |
| Vascular .. .. .. | 8 | 6 | 75 |
| Post-op. .. .. .. | 25 | 6 | 25 |
| Total | 377 | 49 | 13 |

P. J. W. Monks.
Senior Surgical Registrar

TABLE II.—ACUTE SMALL BOWEL OBSTRUCTION
BIRMINGHAM GENERAL HOSPITAL, 1950–1957

| | Cases | Deaths | Mort.% |
|---|---|---|---|
| Simple obstruction .. | 232 | 50 | 21·6 |
| Strangulation obstruction .. | 336 | 14 | 4·2 |
| Total | 568 | 64 | 91·3 |

W. Sewell and M. E. E. White.
Senior Surgical Registrars

the Bristol teaching hospitals from 1952 to 1957, and to the Birmingham General Hospital from 1950 to 1957. These figures show that mesenteric infarction apart, the mortality rate for strangulation obstruction is very much less than for simple obstruction. The former gets expeditious surgery, and the latter, procrastination.

*Post-operative Obstruction*

Few, if any, of the registrars doubted that the post-operative cases of obstruction were among the most difficult to manage. The patient who does well for a few days and then suddenly begins to get colic which continues, is going to need reopening and the sooner the better. The real problem is the patient in whom the usual post-operative ileus has just begun to improve with the return of bowel sounds, when he or she passes into a phase when distension and discomfort increase, slowly and at first without any obvious general deterioration. Post-appendicectomy cases provide a large proportion of these.

Mild cramps occur from time to time and auscultation reveals some sounds and intestinal splashing. By now the patient is being starved and lives on drips whilst gastric suction is either continuous or intermittent. A rising temperature has been brought down by antibiotics of one sort or another, and each day we hope to find these things better. In some cases the light inflammatory adhesions resolve, the ileus passes off, the alimentary noises make music once again, and everyone is happy. In others the unsatisfactory state persists, and an antibiotic intra-abdominal abscess may be established and walled off by adherent omentum and intestinal coils. A collection of pus which should have been drained is now causing true mechanical obstruction; only surgical relief will cure it. By now our patient has begun to deteriorate a little in spite of all our attentions. The veins are used up as indeed may be the poor fellow's morale and resiliency. Now after seven, ten, fourteen days or even longer we feel driven to do something. With a further burst of activity on everybody's part the operation is done and perhaps, after another prolonged fight, the man recovers, or perhaps he does not. We have seen fine young lives lost in this way and we have heard of many more.

Our capacity to maintain these cases in apparently good condition undoubtedly leads to difficulties in making the decision when to interfere. Murphy used to say: "Procrastination kills more patients than cancer." Had we been driven to earlier surgery it might have been better.

"There can be few greater disappointments in life than to lose a patient who has had an otherwise successful gastrectomy or colectomy from a post-operative obstruction." I quote from a memorandum from Leicester, and we would all agree.

It is want of courage to admit to ourselves or to the patient and the relatives that something has gone wrong. How well such patients withstand further expeditious simple surgery and next day how delighted everyone is, including the surgeon.

*The Problem of the Old People*

All the registrars seemed to find that the really old folk provided much anxiety, and too often died whatever was done. The precise cause of death seemed unrelated to the necessary surgery but I feel sure that even here in many cases a happier result would have followed skilful expeditious intervention with early ambulation *and no tubes*. In his letter to me Mr. F. O'Gorman wanted emphasis laid on the uselessness of getting them out of bed only to let them slump in a chair with legs dependent, until assisted back to bed with their veins thrombosed! Operations on the elderly must carry unpredictable risks; some disappointments are inevitable.

The pædiatric surgeons have made a special contribution in their field. The fine work of the Newcastle school has brought about a real reduction in the mortality from late cases of acute intussusception where resection is necessary. As against that, the incidence of mesenteric infarction steadily increases. Judged by the Registrar-General's report it is now over 400 a year. From every centre canvassed the mortality from mesenteric infarction is very high (Fig. 2), 40% to 60% or more. In fact, by excluding such cases the overall mortality in many centres was but 10%. Many, perhaps 50%, of these cases suffer varying degrees of intestinal angina or claudication. They have had pain after meals for which no adequate explanation has been forthcoming. In such cases an aortogram may show extreme narrowing of the superior mesenteric artery just at its origin, the remainder of its length being satisfactory. It has been shown that this defect alone is probably compensated for by collaterals, provided the cœliac axis is free from similar narrowing. If, however, there is coincident disease there, then a massive infarction is in the offing. "Intestinal claudication" after meals will occur, and the outlook is ominous indeed. A very localized endarterectomy, a graft or bypass, might save the inevitable disaster.

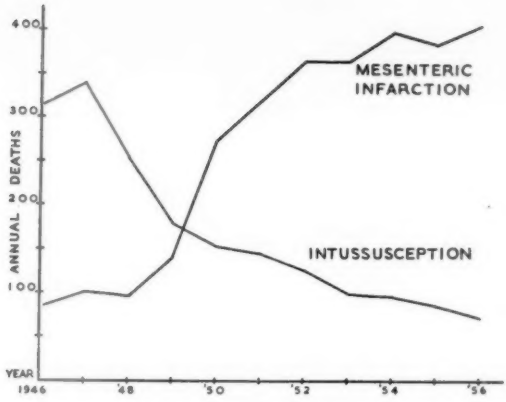



FIG. 2

*Conclusion*

This vast subject is still full of interest and challenge. I have touched on a few things and said next to nothing about technique and technical faults which still contribute their quota of tragedies. Whatever the outcome of our deliberations I am sure the time will have been well spent if only each one of us is determined afresh to see to it that no one, student, resident, registrar, or doctor, leaves our sphere of influence without a clear and vivid picture of the clinical diagnosis of early acute obstruction of the small intestine, and that we as surgeons refrain from trying to be too clever in dealing with it.

**Mr. P. T. Savage** (London):

Mr. P. T. Savage presented a small personal series of 115 cases of small bowel obstruction (excluding external hernia) occurring over the past ten years. There were 17 deaths, a mortality of 16%. Many of the patients were elderly (31 over the age of 70). In those under the age of 70, the mortality was 7%: in those over the age of 70, it was 34%. In 25 cases, the small bowel was gangrenous. The mortality in this group of cases was 24%, but in those under the age of 70, it was only 6%.

*Diagnosis*

In the diagnosis of small bowel obstruction the value of a careful history and an unhurried physical examination, not forgetting an inspection of the vomit, was stressed. The value of erect and supine radiographs of the abdomen was illustrated by a number of films. It was pointed out, however, that in some cases of strangulation obstruction, there was little or no distension of the bowel above the site of the obstruction, and that in these cases, the X-rays showed no characteristic small bowel pattern and no fluid levels. In some cases of simple occlusion, the bowel above the obstruction was distended with fluid and no gas, and in these cases, the X-rays showed only a uniform opacity more suggestive of ascites than obstruction. These "false negative" X-rays constitute, however, only about 5% of all cases, and it was considered that radiography formed a valuable, almost indispensable, logical extension to the physical examination of the abdomen. It was of value not only in diagnosing the presence or absence of obstruction, but also in localizing its site.

The diagnosis of strangulation, as opposed to simple obstruction, was not always easy. Severe and often continuous pain accompanied by abdominal tenderness and later followed by abdominal rigidity, disappearance of bowel sounds, and signs of circulatory collapse were indicative of a strangulation obstruction. On the other hand, a long history (three to five days), a relatively fit patient with considerable abdominal distension, obstructive bowel sounds, and lack of abdominal tenderness and rigidity did not necessarily mean that the cause was a simple occlusion. 3 such cases had occurred in this series, in which at operation a gangrenous and disintegrating loop had been found: one of the cases was described in detail.

*Management*

It was advocated that operation should be carried out in almost all cases just as soon as

the patient could be made fit for operation. In strangulation obstruction with severe circulatory collapse, rapid blood transfusion would often render a moribund patient fit for an unhurried resection and anastomosis. The circulatory collapse in these patients was due to loss of whole blood into the infarcted loop of intestine and to loss of blood-stained fluid into the peritoneal cavity, and not to any hypothetical toxin absorbed into the blood stream. These patients required about a pint of blood for every 12 in.–18 in. of gangrenous intestine. The correction of fluid and electrolyte imbalance in simple occlusion was equally important, but was far too well understood to require further comment.

An extensive trial of Miller-Abbott intubation was carried out in the early part of this series of cases, but it was found to be so unsatisfactory that it had been completely abandoned in favour of decompression of the distended bowel at operation. After much experiment, the intestinal decompressor shown in Fig. 1 was evolved. Suction is applied by means of

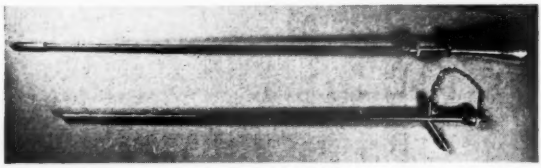


FIG. 1.—Savage's intestinal decompressor (made by Messrs. Thackeray, Leeds).

the angled side-arm, the trocar end of the instrument being introduced into the distended small bowel, just above the level of the obstruction. The trocar is then withdrawn, and the end of the instrument closed with the screw plug. The intestine is then threaded over the instrument in much the same way as a curtain is threaded over a curtain rod, the degree of suction applied being controlled with a thumb placed over the side vent. Surprising though it may seem, it is quite possible to thread the whole of the small bowel over the 14 in. of the working length of the decompressor. At the end of the decompression, the hole in the small bowel is closed by two layers of interrupted silk sutures, placed at right angles to the long axis of the gut. The decompressor has been in use for just over three years, and it has proved to be an easy, quick and very effective method of emptying the small bowel with little or no contamination. Among the more immediate advantages of its use are the ease with which the abdomen can be closed, and the freedom of respiration in the post-operative period. If the stomach is emptied with a tube before the induction of anæsthesia, inhalation of vomit on recovery from the anæsthetic becomes virtually impossible.

*Operative Procedures*

The operative procedures carried out for the relief of obstruction were reviewed. Division of bands and adhesions had been carried out in 53 cases, and resection and end-to-end anastomosis in 33. In 4 infants under the age of 9 months (3 with gangrenous intussusception) resection and immediate anastomosis had been carried out without complication, and it was felt that a 2-stage Paul Mikulicz type of resection was quite unnecessary.

The question of immediate resection and anastomosis in cases of small bowel obstruction in which the bowel was not gangrenous, for example, in Crohn's disease and carcinoma of the cæcum with ileo-cæcal valve obstruction, was discussed. It was considered to be quite safe provided the patient's general condition permitted, and that the small intestine above the anastomosis was decompressed by the method already outlined. Two such cases were described.

# Section of Obstetrics and Gynæcology

President—Sir ARTHUR GEMMELL, M.C., T.D., M.A., M.D., Hon. M.M.S.A., F.R.C.S.Ed., F.R.C.O.G.

[*March* 28, 1958]

## Culdoscopy

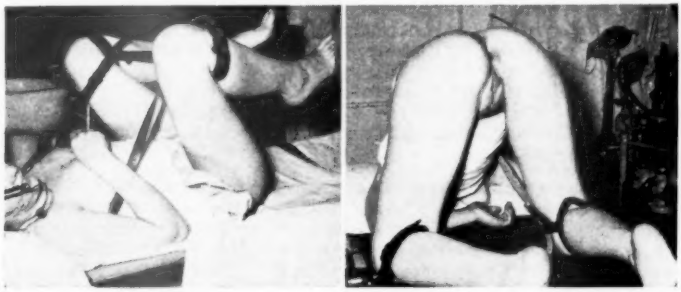
By T. N. A. JEFFCOATE, M.D., F.R.C.S.Ed., F.R.C.O.G.

*Department of Obstetrics and Gynæcology, University of Liverpool*

ALTHOUGH peritoneoscopy (celioscopy, laparoscopy) via the abdominal wall has been carried out for nearly fifty years, the successful use of an endoscope passed through the pouch of Douglas was first reported by Decker and Cherry of New York in 1944. It was these workers who gave the procedure its name of culdoscopy. This is now widely practised both in North America and the European continent. So far, however, it has found little favour in this country; there has even been prejudice against it. I, for one, could see little place for the operation until, late in 1955, I was forced to perform it as one of my duties while working abroad. The experience was so impressive that the culdoscope was subsequently introduced to my own unit where, for almost two years, it has been used by myself and by two members of staff in selected cases. Not all the cases were well selected so that puncture of the pouch of Douglas failed in 4 out of 44 cases. This is an unnecessarily high failure rate. In 2 failures, one of ruptured endometriomatous cyst and one of septate vagina and uterus didelphys, the indication was mainly curiosity.

*Technique.*—The technical details of culdoscopy are described by Decker (1952). The secret of success and safety is to place the patient in the knee chest (not knee elbow) position. Because of this most operators keep the patient conscious, using only saddle block or local infiltration (combined if necessary with pudendal block) anæsthesia. So far, and bearing in mind the natural apprehension of patients and my own lack of experience, I have not depended on local analgesia. Low spinal block can be very satisfactory but the patient occasionally finds herself losing complete control over her legs and fails to keep position, also vomiting and straining are not uncommon. Because of such happenings, and especially because most women in this country find the knee chest position embarrassing, general anæsthesia was used in all except 4. The difficulty of maintaining the knee chest position in an anæsthetized woman is well known. For culdoscopy I turned to a method which I have used for other purposes for many years.

The old Clover's crutch is employed to fix the attitude of the already anæsthetized patient and she is then rolled over from a trolley into position on an ordinary operating table[1] (Fig. 1). The thighs should not be too sharply flexed on the trunk. Before turning the



A B

FIG. 1A, B.—The use of Clover's crutch for maintaining the knee chest position for culdoscopy under general anæsthesia. A, Crutch applied and patient ready for bimanual examination and catheterization; B, Patient rolled into position for culdoscopy.

[1] The table has to be moderately wide otherwise the bar of the crutch forces the patient's knees over the sides.

patient, it is important to carry out a bimanual examination to exclude as far as possible the presence of lesions such as a fixed retroversion which might distort or obliterate the utero-rectal pouch. The bladder is also catheterized at this time.

A doubled pillow is used to protect the chest and shoulders from the hard impact of the table. Endotracheal anæsthesia is essential to maintain adequate oxygenation. One advantage of this simple yet efficient method of securing the knee chest position is that it leaves the abdominal wall completely free from pressure, accessible to the operator's left hand should he wish to manipulate the pelvic organs to bring them into view. It also ensures an adequate pneumoperitoneum.

Cystic ovaries, a recent corpus luteum, adhesions and other lesions can be recognized as easily as at laparotomy. The operation can be combined with tubal patency tests, curettage and gynæcography; the last, however, does not usually provide any additional information. Curettage is a specially valuable adjunct since it permits a comparison of the endometrial and ovarian pictures.

*Sequelæ.*—Following culdoscopy nearly all patients complain of pain for two or three days in the hypochondrium and shoulders. It is probably not due to the harness of the crutch, or to the position but to the pneumoperitoneum (and possibly pneumomediastinum). We have used air rather than carbon dioxide and have not taken any steps to encourage its escape before removing the cannula.

Three of our patients developed œdema of the eyelids; this was present at the end of the operation but disappeared completely within twenty-four hours; in one the forehead showed petechiae and ecchymoses. This proved to be of more than passing interest because the patient's complaint was menorrhagia for which all manner of investigations (including culdoscopy) had not revealed a cause. The petechiae led to the recognition of a state of capillary fragility which almost certainly accounted for the uterine bleeding.

No major complications occurred and, apart from the shoulder discomfort, the women suffered no inconvenience. Where laparotomy was carried out a few days later it was impossible or difficult to find any trace of the puncture hole in the Pouch of Douglas.

*Indications and results.*—An objection to the practice of culdoscopy is that it is easily abused. Instead of reaching a diagnosis as a result of analysing symptoms and signs, the lazy-minded gynæcologist is tempted to "look and see". Culdoscopy has potential, if not real, hazards and should therefore only be used when standard diagnostic methods fail and when there is no clear indication for laparotomy. We employed it at an average rate of once in three weeks for the indications shown in Table I.

TABLE I.—INDICATIONS FOR CULDOSCOPY

| | 40 cases |
|---|---|
| Infertility (previous investigations negative or doubtful) | 17 |
| Virilism of varying degrees | 11 |
| Amenorrhœa and oligomenorrhœa | 3 |
| Irregular and excessive uterine bleeding | 3 |
| Possible ectopic pregnancy | 3 |
| Pelvic pain | 2 |
| Small pelvic tumour, nature uncertain | 1 |

*Infertility.*—The major indication was unexplained infertility (17 cases). Culdoscopy revealed the cause in more than half of these (*see* Table II). Of the remaining 8 women in whom there was no visual pelvic abnormality it is known that at least 3 have subsequently conceived; another was shown, by curettage carried out at the time of culdoscopy, to have endometrial tuberculosis.

TABLE II.—CULDOSCOPIC FINDINGS IN 17 CASES OF INFERTILITY

| | | |
|---|---|---|
| Peritubal adhesions | 4 | (2 previously said to be normal) |
| Tubal obstruction | 2 | |
| Endometriosis | 1 | (said to be normal) |
| Rudimentary horn and tube | 1 | (said to be unicornuate uterus) |
| Tubal tuberculosis | 1 | (endometrial studies negative) |
| No abnormality* | 8 | (one previously said to have closed tubes. At least 3 have become pregnant since) |

* Simultaneous curettage resulted in an ultimate diagnosis of endometrial tuberculosis in one case.

Culdoscopy makes it easy to recognize obstruction of the ovario-tubal pathway by adhesions but the assessment of tubal patency necessitates injecting a coloured medium such as indigo-carmine solution through the cervix. This was done in 8 cases. Although it is not always possible to see the tubes throughout their length, the escape of such a dye from their outer ends is readily recognized.

One patient had been investigated for infertility in two clinics. A diagnosis of pelvic tuberculosis was suspected because of the family history but could not be established. All the findings, even bacteriological studies of the endometrium, were normal. Yet culdoscopy revealed clear evidence of a caseating nodule in one tube.

*Virilism.*—The second most common indication was virilism usually of the mild variety (Table III). The woman who is hirsute and oligomenorrhœic presents a common clinical problem and it can be extremely difficult, by ordinary clinical methods and by hormone assay, to exclude a small ovarian lesion as a cause. One of the first patients on whom culdoscopy was carried out proved to have an arrhenoblastoma which was not palpable during examination under anæsthesia, and which produced atypical symptoms. Even when a small tumour is palpable its nature and significance may be doubtful. Culdoscopy is one of the best methods for recognizing the multiple cystic ovaries characteristic of the Stein-Leventhal syndrome, and for recognizing that the ovaries are functioning normally in cases of constitutional hirsutism.

TABLE III.—CULDOSCOPIC FINDINGS IN 11 CASES OF VIRILISM

| | |
|---|---|
| Bilateral cystic ovaries (Stein-Leventhal syndrome) | 3 cases |
| Arrhenoblastoma | 1 case |
| No abnormality (recent corpus luteum in 2) | 7 cases |

*Other indications.*—The value of culdoscopy to elucidate other symptoms, such as abnormal uterine hæmorrhage of obscure origin, requires no elaboration. The enthusiasts for the procedure emphasize its usefulness in the diagnosis of ectopic pregnancy and endometriosis. If endometriosis is suspected culdoscopy is usually contra-indicated because of the likelihood of there being adhesions behind the uterus. Moreover, ectopic pregnancy can usually be recognized without culdoscopy. Nevertheless, the positive exclusion of such a condition can sometimes be very reassuring to patient and attendant alike.

Indeed, our limited experience suggests that, providing reasonable care is taken over clinical methods of diagnosis, the main practical value of culdoscopy is as a means of excluding rather than finding local disease in the pelvic organs. In one-half of our cases no abnormality was seen (Table IV) but a negative finding was just as valuable, if not more

TABLE IV.—SUMMARY OF CULDOSCOPIC FINDINGS

| | Cases |
|---|---|
| Peritubal and other adhesions | 6 |
| Tubal disease | 3 |
| Cystic ovaries (Stein-Leventhal syndrome) | 3 |
| Follicular cyst | 3 |
| Tubal pregnancy | 2 |
| Endometriosis | 1 |
| Arrhenoblastoma | 1 |
| Gonadal agenesis | 1 |
| Rudimentary uterine horn | 1 |
| No abnormality (recent corpus luteum in 4) | 19 |
| Total | 40 |

valuable, in their handling than if a pathological state had been found. In gynæcological practice it is generally easy to make a positive diagnosis but often difficult to say for certain that an organic lesion is not present. Culdoscopy finds its place in the investigation of those patients in whom the chances of finding a pathological state requiring surgery are so slight that laparotomy is not justified.

*Conclusion.*—The very last patient in this series serves to emphasize the value of the procedure. A woman twice married and aged 31 complained of three years' infertility following 2 abortions. Hysterography revealed a typical uni-cornuate uterus with doubtful patency of the one tube. Post-abortal peritubal adhesions were suspected. Culdoscopy revealed that the tube was open and free from adhesions but that the uterus was not unicornuate. There was a second rudimentary horn and tube not communicating with the cervix. Both ovaries were normal, the one on the side of the rudimentary Müllerian duct containing a recent corpus luteum. The preceding ovulation was obviously wasted, the ovum not having a functional oviduct to receive it. Subsequent removal of the rudimentary horn together with the ovary on the same side should double this patient's chances of pregnancy because subsequent ovulation will take place on the side where there is a well-developed tube and uterine horn.

Our experience, although limited to two years, leads to the conclusion that there are certain selected cases in which culdoscopy is of the greatest value in determining diagnosis and treatment. The selection of cases does, however, require to be strict, from the standpoint of need and safety. The operation is so easy to perform that it can be abused. This, however, is not a reason for denying it a rightful place in gynæcological practice.

REFERENCES

DECKER, A. (1952) Culdoscopy. Philadelphia and London.
—— and CHERRY, T. (1944) *Amer. J. Surg.*, **64**, 40.

## Amnion Nodosum

By J. S. SCOTT, M.B., M.R.C.O.G.
*Department of Obstetrics and Gynæcology, University of Liverpool*
and
A. D. BAIN, M.D.
*Department of Pathology, University of Edinburgh*

DURING the course of a detailed inspection of the placenta and membranes from over 3,161 consecutive deliveries at Mill Road Maternity Hospital, Liverpool in 1956–57, a nodular condition of the fœtal surface of the amniotic membrane was observed in two instances. The amniotic lesion consisted of small nodules 1–2 mm. in diameter which in areas coalesced to form larger plaques. In colour they varied from pink to yellow. They were more obvious on that portion of the amnion which covered the placenta and could be moved with the amniotic membrane over the placental surface. One of their most striking features was that they could be picked off the underlying membrane.

Histologically the nodules were found to consist of masses of keratinized squames embedded in an amorphous acidophil matrix. The columnar cells of the amniotic epithelium were atrophied in the region of the nodules and there was no evidence of squamous metaplasia of the amnion.

It was most remarkable that both instances of the condition occurred in cases in which the baby had bilateral renal agenesis and in which oligohydramnios had been noted clinically. Both babies showed the classical facial appearances of renal agenesis.

The placentae and membranes were then examined by one of us (A. D. B.) from a further 8 perinatal autopsies in Edinburgh and South Eastern Scotland, in which bilateral renal agenesis, or severe cystic dysplasia with absence of renal function, was found. In all but one case the same amniotic abnormality was noted—and, with the exception of this single case, clinical observations of definite or suggestive liquor deficiency had been entered in each case record. The exception was a case in which the baby also had iniencephaly and in this instance there was hydramnios, confirmed by abdominal paracentesis.

These lesions correspond to those described by Landing (1950) under the title of "amnion nodosum". He reported 8 cases, 5 associated with major urinary abnormalities in the fœtus.

Two lesions may be mistaken for amnion nodosum:

(i) *Small subchorionic fibrin deposits.* The amnion can be made to slide *over* these deposits.

(ii) *Squamous metaplasia of the amnion.* In this condition there is a more diffuse thickening of the amnion; the plaques can *not* be separated from the membrane and, histologically, the squamous metaplasia is obvious.

*Cause of amnion nodosum.*—The problem arises as to whether the amniotic lesions are embryonic defects related to the renal agenesis or whether they are secondary to the oligohydramnios which is an almost constant accompaniment of renal agenesis. 50 case records of renal agenesis were reviewed from this aspect with the following findings:

| | cases |
|---|---|
| Deficiency or absence of liquor specifically noted | 7 |
| Suggestive evidence of liquor deficiency | 28 |
| Relevant information not recorded | 14 |
| Liquor present | 1 |

Our findings confirm those of Potter (1953) who failed to find an obstetrician who had seen liquor escape from the uterus in 30 cases of renal agenesis which she reported.

From these observations and those of Scott and Wilson (1957) on the relationship of hydramnios to lesions interfering with fœtal swallowing, we conclude that fœtal micturition and swallowing play a major part in the control of the volume of liquor in late pregnancy.

In one case of oligohydramnios *not* associated with renal agenesis, the amnion showed a fine granular appearance, which on section proved to have the appearances of amnion nodosum.

From the available evidence it appears that the absence of liquor, by allowing the fœtus to come into direct contact with the amnion, leads to transfer of fœtal squames to the amnion by a detritic mechanism.

*Clinical features.*—One consequence of the oligohydramnios associated with renal agenesis is a high incidence of breech presentation in labour. In our series the figures were:

| Presentation | Cases |
|---|---|
| Breech | 30 |
| Vertex | 19 |
| Not recorded (Cæsarean section) | 1 |
| Total | 50 |

This 60% incidence of breech presentation is not explained by prematurity—36 out of 50 babies being delivered after the 34th week.

The diagnosis of renal agenesis should be suspected in the antenatal period if, towards term, the uterus fails to enlarge as expected, liquor seems deficient and the fœtus small. Indeed the picture is one of "placental insufficiency" but there is no obvious cause for this such as chronic hypertension.

The baby will often be presenting by the breech in labour and the obstetrician may be distressed to find the child dead or dying after an uneventful breech delivery. Recognition of the typical facies of renal agenesis may relieve his anxiety but in cases of doubt inspection of the membranes for signs of amnion nodosum may settle these long before the child comes to post-mortem examination.

*Acknowledgments.*—We are indebted to Dr. E. G. Hall for the autopsy reports on the cases occurring at Mill Road Maternity Hospital.

REFERENCES

LANDING, B. H. (1950) *Amer. J. Obstet. Gynec.*, **70**, 1339.
POTTER, E. (1953) Pathology of the Fœtus and the Newborn. Chicago.
SCOTT, J. S., and WILSON, J. K. (1957) *Lancet*, ii, 569.

## Pregnancy in Addison's Disease

By H. H. FRANCIS, F.R.C.S., M.R.C.O.G., and J. E. FORSTER, M.B., M.R.C.P.
*Departments of Obstetrics and Gynæcology and Medicine, University of Liverpool*

THE well-being and life span of patients with Addison's disease have been greatly improved by cortisone and allied substances. Prior to 1951 their average expectation of life was only two and a quarter years or three and a half years depending on whether tuberculous infection or atrophy was the cause, but women with Addison's disease can now expect to survive the entire reproductive period and to enjoy almost normal fertility. Pregnancy, and, in particular, labour and its complications were hazardous in the past (Cohen, 1948; Plotz, 1953), but only 1 maternal death has been recorded (Stein, 1955) amongst 13 cases when cortisone was given (Wells and Wesp, 1952; Rolland, *et al.*, 1953; Hunt and McConahey, 1953; Andersson, 1953; Gurling, Rackow and Smith, 1954; Hendon and Melick, 1955; Moore and Freedman, 1956; Kaiser, 1956; Beaulieu, Bricaire and Jayle, 1956; Singh, 1957; Beckett and Evans, 1957; Bergman and Skanse, 1957).

### CASE HISTORIES

*Case* 1.—Aged 28. Para 2.

Treated by increased salt intake and deoxycortone trimethylacetate for two years prior to conception. Vomiting led to readmission in crisis at 8 weeks and 24 weeks gestation. Cortisone, 25 mg. daily, was followed by sustained improvement. Cortisone 100 mg. daily was commenced near term, and maintained until three days after delivery. Labour and the puerperium were uneventful. The baby weighed 7 lb. 14 oz.

*Case* 2.—Aged 32. Para 3.

Adrenal insufficiency had been controlled by increased salt intake and deoxycortone implants for seven months when conception occurred. Vomiting led to exacerbations of Addison's disease requiring in-patient treatment at 8 weeks and 26 weeks maturity. Cortisone, 25 mg. daily, resulted in sustained improvement.

Spontaneous delivery of a child weighing 7 lb. 12 oz. after a labour of only three hours was followed by post-partum hæmorrhage of 30 oz. The patient collapsed and recovery was very slow in spite of adequate blood transfusion and large doses of deoxycortone and aqueous adrenal extract. Cortisone 25 mg. was given intramuscularly. The blood pressure reached 90/60 after four hours. Cortisone 25 mg. intramuscularly twelve-hourly, and deoxycortone 10 mg. intramuscularly six-hourly, proved inadequate and twenty-six hours after delivery a second collapse occurred. Despite cortisone 600 mg. intramuscularly during the next six hours, and adequate mineralocorticoid and glucose-saline, the blood pressure remained unrecordable for eight hours, and only reached 70/40 six hours later. Thereafter, with increasing absorption from the intramuscular depot of cortisone, recovery was uneventful.

*Case* 3.—Aged 28 years. Primigravida.

One year before Addison's disease was recognized, she had been investigated elsewhere for five years' infertility with negative findings. Seven weeks after leaving hospital on cortisone, sodium chloride and deoxycortone treatment, conception occurred. This therapy was maintained unchanged until 30 weeks' gestation, when the appearance of ankle œdema caused the extra salt and deoxycortone trimethylacetate to be stopped.

Labour commenced at term and cortisone 50 mg. was given intramuscularly on three occasions during the first stage, before fœtal distress demanded Cæsarean section. Lower segment operation was performed under local infiltration with 150 ml. of lignocaine 0·5%, supplemented with nitrous oxide and oxygen for delivery of the head and suturing. An intravenous infusion of hydrocortisone was commenced prior to operation and continued for thirty-six hours, the rate being controlled by hourly blood pressure readings. The total dose was 150 mg. Oral cortisone was then recommenced and gradually reduced to the previous maintenance level. Wound healing was normal.

The child weighed 3 lb. 12 oz. and showed bilateral lid retraction with moderate exophthalmos for thirty-six hours. The placenta weighed only 13 oz. but showed a normal microscopic appearance and no cause for the fœtal distress was found.

*The management of pregnancy.*—The pre-pregnancy dose of cortisone must be maintained unchanged throughout the pregnancy, as a reduction, even late in the third trimester, will be followed by the return of Addisonian symptoms (Hills *et al.*, 1954; Halberg and Kaiser, 1954). Furthermore, any additional stress such as vomiting, infection or hæmorrhage must be met by a temporary increase in the maintenance dose (Fig. 1). The work of Beaulieu *et al.* (1956) and Kaiser (1956) shows that the adrenals of patients with Addison's disease are unable to secrete the additional corticosteroids which are recovered from normal patients during pregnancy, and which Bayliss *et al.* (1955) ascribe to the maternal adrenal as opposed to the placenta.

During the last trimester there is a reduction in the demand for additional sodium chloride (Kaiser, 1956). When maintenance therapy has included a mineralocorticoid, this should be curtailed (Thorn *et al.*, 1942), but prompt resumption is required after delivery (Rolland *et al.*, 1953) (Fig. 1). This suggests some mineralocorticoid production by the placenta.

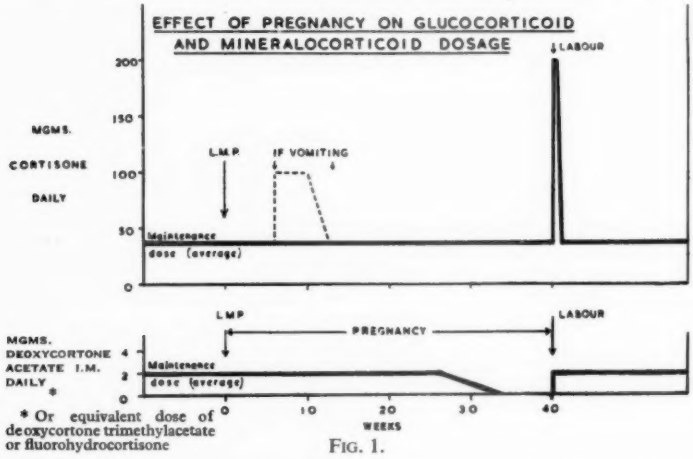



FIG. 1.

As deoxycortone implants retain their activity for approximately six months, none should be given after pregnancy has been diagnosed. Deoxycortone trimethylacetate is effective for one month and is therefore being replaced by oral fluoro-hydrocortisone as the dosage can be readily adjusted to meet the diminishing needs in the last trimester.

*Management of labour and the puerperium.*—An adrenal crisis is more likely to develop during the first twenty-four hours after delivery than at any other time during the child-bearing incident (Cohen, 1948; Davis and Plotz, 1956; Moore and Freedman, 1956). This results from inability of the adrenals to meet the stress of labour. The loss of biologically active placental steroids has been suggested as an additional factor, but is as yet unproved. The muscular exertion of labour may be an important factor. To prevent this reaction, cortisone 200 mg. daily during labour and the first forty-eight hours after delivery is recommended. It should be given as 50 mg. six-hourly, intramuscularly during labour, and orally thereafter. This dosage is sufficient to meet the minor complications of labour. The blood pressure, as determined by hourly readings, is the best guide to the adequacy of the dosage, a fall indicating the need for further cortisone. Blood serum electrolyte and sugar determinations are of less value as controls. After the first two days of the puerperium the dose of cortisone is gradually reduced to the previous maintenance level, the blood pressure being checked four-hourly.

It is not always appreciated that the rate of absorption of cortisone injected intramuscularly is much slower than when given by mouth, in fact the interval between doses of oral cortisone should not exceed eight hours. By the intramuscular route the absorption peak is not reached for six to 10 hours and the effect lasts for more than twenty-four hours. If a rapid effect is required and the oral route is not available as in crises, in preparation for major obstetrical manœuvres or in the treatment of major complications, intravenous hydrocortisone must be used. It is given by continuous infusion in glucose-saline and controlled by blood pressure readings. The second case, which occurred prior to hydrocortisone becoming available, illustrates this point.

Cæsarean section must not be undertaken to spare the patient the stress of labour, as Addisonian patients are intolerant of all operative procedures. The mortality of even minor operations was 100%, prior to the advent of aqueous adrenal extract (Greene *et al.*, 1933). The summation of the obstetrical and surgical risks is illustrated by the recorded fatalities following operative termination of pregnancy (Thorn *et al.*, 1942; Van Zwanenberg, 1945; Cohen, 1948) and following Cæsarean section (Cohen, 1948; Brent, 1950). In fact only 5 survivals following Cæsarean section are recorded in the pre-cortisone era (Knowlton *et al.*, 1949; Franks, 1950; Schwartz *et al.*, 1952; Lutwyche, 1953; De Gennes *et al.*, 1956) and one survival under cortisone control (Hunt and McConahey, 1953).

Regarding the administration of mineralocorticoids during labour, opinion is divided, and the dose should therefore be limited.

The second case illustrated the intolerance of these patients for post-partum hæmorrhage, suggesting the prophylactic use of ergometrine at the end of the second stage.

It was general experience before the availability of cortisone that patients with Addison's disease were unduly sensitive to analgesic and anæsthetic drugs. Wells and Wesp (1952) observed an apparent decrease in the tolerance for pethidine and barbiturate in the first reported case of pregnancy under cortisone control. However, all 3 patients in this series exhibited normal tolerance to pethidine, and the third to nitrous oxide anæsthesia, although caution was always shown with the dosage. Papper and Cahill (1952) and Dundee (1957) showed that patients receiving adequate substitution therapy tolerate analgesics and anæsthetics normally.

It will be apparent that similar management will be required by obstetrical patients whose adrenals have been surgically removed, and, for a shorter period, by those with acute adrenal insufficiency due to the suppressive effect of previous cortisone therapy.

Lactation failed in all of our cases, although the evidence in one was vitiated by the administration of œstrogen. Adrenal glucocorticoids appear to be essential for mammary function (Mason, 1957). This however, implies that whereas failure was the general experience in the past, breast feeding may be possible in the future.

The progress of all 3 babies was normal. This and the normal serum electrolyte levels found in the only baby investigated confirm other reports that there is no evidence of antenatal over-activity of the fœtal adrenals in an effort to contribute to the mother (Jailer and Knowlton, 1950; Hendon and Melick, 1955; Bergman and Skanse, 1957). All of the babies were free from permanent congenital defects. The transient eyelid retraction and exophthalmos observed in the third baby immediately after birth, become an interesting feature when considered in conjunction with the experimental production of exophthalmos by administering large doses of cortisone to adult rats (Aterman and Greenberg, 1953) and of congenital exophthalmos by similar treatment of pregnant female rats (Davis and Plotz, 1956).

*The future.*—Pregnancy in Addison's disease was previously rare, less than 100 cases being reported (Davis and Plotz, 1956). Rolland *et al.* (1953), found only 2 cases amongst 60,000 deliveries. The third case in this series is the only one recorded amongst 80,000 deliveries in forty-two years at the Liverpool Maternity Hospital. The other 2 cases

were delivered in regional hospitals where records of the cases of Addison's disease encountered over the years are not readily available. Cortisone appeared to cure this patient's infertility as she conceived within seven weeks of leaving hospital after having been infertile for six years, during the last nine months of which she was showing obvious signs of Addison's disease. Of the 13 patients reported to date as receiving cortisone therapy during part or all of their pregnancies, 3 were under cortisone treatment at the time of their marriage and all conceived shortly thereafter, 2 within three months (Hunt and McConahey, 1953; Hendon and Melick, 1955; Beckett and Evans, 1957). On the other hand, modern antibiotics should almost eliminate the spread of tuberculous infection to the adrenals, previously the source of one-half of the cases. However, simple atrophy will still provide new cases and, irrespective of the cause, cortisone will so enhance the well-being, the fertility and expectation of life of those with chronic adrenal insufficiency that an absolute increase in the number of patients with this disability and pregnancy should result.

We wish to thank Dr. P. L. Robinson and Mr. J. A. Bentham for permission to present the first case, Dr. D. M. Freeman and Dr. G. W. Millington for the second case and Lord Cohen of Birkenhead, Dr. E. T. Baker-Bates and Professor T. N. A. Jeffcoate for the third case. We are deeply grateful fo Professor T. N. A. Jeffcoate for his help and valuable criticism and to Dr. J. D. N. Nabarro who kindly commented on this paper.

## REFERENCES

ANDERSSON, B. (1953) *Nord. med.*, **49,** 172.
ATERMAN, K., and GREENBERG, S. M. (1953) *Endocrinology*, **52,** 510.
BAYLISS, R. I. S., BROWNE, J. C. M., ROUND, B. P., and STEINBECK, A. W. (1955) *Lancet*, i, 62.
BECKETT, A. G., and EVANS, M. R. E. (1957) *Brit. med. J.*, i, 1302.
BEAULIEU, E. E., BRICAIRE, H., and JAYLE, M. F. (1956) *J. clin. Endocrin.*, **16,** 690.
BERGMAN, P., and SKANSE, B. (1957) *Nord. med.*, **57,** 390.
BRENT, F. (1950) *Amer. J. Surg.*, **79,** 645.
COHEN, M. (1948) *Arch. intern. Med.*, **81,** 879.
DAVIS, M. E., and PLOTZ, E. J. (1956) *Obstet. Surv. Baltim.*, **11,** 1.
DE GENNES, L., BRICAIRE, H., HAZARD, J., and BEAULIEU, E. (1956) *Pr. méd.*, **1,** 689.
DUNDEE, J. W. (1957) *Brit. J. Anæsth.*, **29,** 166.
FRANKS, R. B. (1950) *St. Thom. Hosp. Rep.*, 2nd Series, **6,** 136.
GREENE, C. H., WALTERS, W., and ROWNTREE, L. G. (1933) *Ann. Surg.*, **98,** 1013.
GURLING, K. J., RACKOW, F., and SMITH, M. J. (1954) *Lancet*, ii, 316.
HALBERG, F., and KAISER, I. H. (1954) *Acta endocr., Copenhagen*, **16,** 227.
HENDON, J. R., and MELICK, R. A. (1955) *J. Kentucky St. med. Ass.*, **53,** 141.
HILLS, A. G., VENNING, E. H., DOHAN, E. C., WEBSTER, G. D., and RICHARDSON, E. M. (1954) *J. clin. Invest.*, **33,** 1466.
HUNT, A. B., and MCCONAHEY, W. M. (1953) *Amer. J. Obstet. Gynec.*, **66,** 970.
JAILER, J. W., and KNOWLTON, A. I. (1950) *J. clin. Invest.*, **29,** 1430.
KAISER, I. H. (1956) *J. clin. Endocrin.*, **16,** 1251.
KNOWLTON, A. I., MUDGE, G. H., and JAILER, J. W. (1949) *J. clin. Endocrin.*, **9,** 514.
LUTWYCHE, V. U. (1953) *Brit. med. J.*, i, 313.
MASON, A. S. (1957) Introduction to Clinical Endocrinology. Oxford, pp. 164, 95.
MOORE, F. H., and FREEDMAN, J. R. (1956) *Amer. J. Obstet. Gynec.*, **72,** 1340.
PAPPER, E. M., and CAHILL, G. F. (1952) *J. Amer. med. Ass.*, **148,** 174.
PLOTZ, E. J. (1953) *Klin. Wschr.*, **31,** 831.
ROLLAND, C. F., MATTHEWS, J. D., and MATTHEW, G. D. (1953) *J. Obstet. Gynæc., Brit. Emp.*, **60,** 57.
SCHWARTZ, H., DERRICK, W. S., and PAPPER, E. M. (1952) *Surg. Gynec. Obstet.*, **94,** 455.
SINGH, M. M. (1957) *Brit. med. J.*, i, 503.
STEIN, F. (1955) *Beitr. path. Anat.*, **115,** 102.
THORN, G. W., DORRANCE, S. S., and DAY, E. (1942) *Ann. intern. Med.*, **16,** 1051.
VAN ZWANENBERG, D. (1945) *St. Bart's Hosp. J.*, **49,** 31.
WELLS, C. N., and WESP, J. E. (1952) *Amer. J. Obstet. Gynec.*, **63,** 925.

# Section of Dermatology

President—JOHN T. INGRAM, M.D., F.R.C.P.

[*February* 20, 1958]

**Kaposi's Varicelliform Eruption (Eczema Herpeticum) Treated with Prednisone.**—S. C. GOLD, M.D.

Mr. C. L., aged 21, has been under observation for some years on account of a chronic eczema involving particularly the elbow and knee flexures. This did not develop until the age of 16 but it has many of the features of Besnier's prurigo. From time to time he has had recurrent and trivial attacks of herpes simplex involving his lips.

The present illness started on November 30, 1957, when he felt unwell, shivered, and developed a temperature. Within twenty-four hours he was aware that his eczema was behaving in an unusual way, notably at the back and sides of the neck and the face. He continued to feel unwell, shivering and sweating, and was seen in hospital four days after the onset. At this time a dense eruption of umbilicated pustules of uniform size involved the neck, his temperature was 101° F., and clinically the eruption suggested Kaposi's varicelliform eruption; the umbilicated lesions were not present on the limbs or arms. Scrapings from the base of a lesion revealed many balloon cells, but he denied any attack of herpes simplex immediately preceding this attack, or of being in contact with anyone known to have had active herpes simplex. It should be mentioned that his father was in bed with pneumonia at this time.

He was admitted to hospital and immediately given systemic prednisone, 20 mg. daily. On account of some secondary infection he was given in the first place oxytetracycline, 2 grams daily; on the eleventh day of his illness the antibiotic was changed to penicillin 1 mega unit daily by injection. Subsequently it transpired that the bacterial flora isolated from his skin were, in fact, resistant to both oxytetracycline and penicillin so that these antibiotics cannot have contributed materially to the dramatic clinical response which was made.

Within forty-eight hours of starting prednisone he felt much better, the fever started to subside and the skin eruption to clear. He was afebrile and remained so after seventy-two hours. Prednisone was maintained, and he is still on a dose of 15 mg. daily.

Herpes neutralization tests showed antibody to be present on the fourth, twelfth and seventeenth days of illness. Two tests were carried out, and both of these revealed the presence of antibody to a uniformly low titre. This level remained constant throughout, a characteristic finding in those suffering from recurrent herpes simplex rather than from an initial herpetic infection.

**Mr. Gold:** The points I would like to make are that this patient, a sufferer from atopic eczema, became superinfected with herpes simplex. He has had many previous trivial attacks of herpes simplex and therefore I judged him to have some natural immunity. At the onset he was acutely ill and I felt that he was a suitable subject for corticosteroids—because if the underlying eczema were suppressed I felt the herpetic infection would probably abate. In fact the results were dramatic. I do not believe the antibiotics given materially influenced his course.

Antibody estimations revealed their presence throughout, their level remaining constant.

I would like to stress that I was aware of theoretical dangers in the course I pursued and I would not recommend such action for a severe and widespread superinfection nor for a primary infection with herpes simplex.

**Dr. R. T. Brain:** I have had a series of 38 cases of eczema herpeticum and the mild cases usually subside in a few days without treatment with an antibiotic drug. Although the pustules were often bacteriologically sterile, it was usual to find the herpes virus in them. The two exceptional cases were vaccinial. I would have hesitated to use the corticosteroids because my experience suggests that they encourage secondary infection. For example, the only adult in the above-mentioned series was a man of 53 who had a relapsing seborrhœic dermatitis of some years' duration. Following a boil, a relapsing phase was being controlled by cortisone when he suddenly became febrile and developed eczema herpeticum. He had necrotic lesions in his axillæ from which Dr. J. A. Dudgeon recovered the herpes virus. He was not subject to eczema. Another instance occurred in a child with alopecia totalis treated with hydrocortisone ointment and his clean scalp became pustular. My impression is that staphylococcal infections are more frequent and more severe in patients being treated with the corticosteroids.

**Dr. Louis Forman:** Steroids suppress inflammatory response to infection and also antibody formation. Where there exists such a severe herpes virus infection there must be a risk of encephalitis. I would wish to be certain that this risk is not increased by treatment with steroids.

**Dr. C. D. Calnan:** I am not at all sure that it is right to say that steroids influence antibody production; the antibodies are formed even while the steroids are being given. All the steroids do is to prevent the inflammatory reactions which may result from the antigen-antibody reaction or some other process.

**Multiple Skin Necroses (Arteriolar)—Ingram and Sutherland.**—MAURICE GARRETTS, M.B., M.R.C.P. (for W. N. GOLDSMITH, M.D., F.R.C.P.).

Mr. A. D., aged 73.

*History.*—"Recurrent boils" for the last twenty-six years. The first attack occurred when the patient was 47 years old. He described several boils which first appeared on the right leg and took one to two months to heal. Since this time he has had crops and single lesions mainly on the legs but also on the hips, trunk, and around the jaw, though by far the greater number occur on the lower extremities. Lesions commence as small pale pink papules which irritate, and rapidly progress, and coalesce to form a hæmorrhagic crust. When the crust separates, an ulcer is left which heals slowly over the course of one to two months, producing a varioliform scar.

The patient has never had longer than eight to twelve months free of lesions in the past twenty-six years. He feels irritable and rather miserable during the attacks, but has no symptoms referable to other systems. He was found to be in the habit of applying neat Dettol to the lesions during 1952, and this practice was discouraged.

Penicillin cream from his own doctor did not help, and occlusive dressings made the condition worse.

*General health.*—Has suffered from duodenal ulcers for the last twenty-four years, and controls his indigestion by using alkaline powders. Appetite, micturition, sleep: normal. Weight steady. Bowels: occasional use of liquid paraffin.

*Family history.*—Mother died of pulmonary tuberculosis twenty years ago. Daughter has suffered from pulmonary tuberculosis for twenty years.

*On examination.*—Afebrile healthy man, with no symptoms other than cutaneous. Several depressed thin white varioliform scars on legs and thighs. One hæmorrhagic crusted lesion on the symphysis pubis.

C.V.S.: Normal. B.P. 130/70. No evidence of arteriosclerosis. Fundi healthy. Urine clear. All pulses palpable. Other systems normal.

*Investigations.*—W. R. and Kahn repeatedly negative. White cell count and differential normal. Hb 100%. Mean cell diameter: 7·2 $\mu$. Mist. hydrarg. perchlor. et pot. iod. was given for two weeks, after which the W.R. and Kahn were found to be negative. Ulcerated areas yielded *Staph. pyogenes* on bacteriological culture. Chest X-rays: normal.

*Biopsies.*—Several biopsies have been taken, and the disorder has been studied at various stages. Certain features are common to all sections, namely, a deep infiltrate of lymphocytes and histiocytes which are mainly perivascular. In the crusted lesion, the epidermis is necrotic and hæmorrhagic, and there is degeneration of the dermis with deep infiltration extending to fat in the more advanced lesions.

Evidence of thrombosis and endarteritis of arterioles has been found in the more advanced lesions, where the structure of the vessels is almost lost in the intense inflammatory response.

*Discussion.*—This man has been regarded as a case of dermatitis artefacta, but against this is the fact that the patient has nothing to gain by prolonging the condition since he retired many years ago. He has "never lost a day's work", and is reluctant "to waste doctor's time" by attending clinics. Recently he has been thought to fit the description "multiple skin necroses" (arteriolar) which was chosen for a man with many similar features by Ingram and Sutherland (1957); this paper records the case of a man of 25 years who presented with a nine months' history of lesions which proceeded through a similar cycle, rather more quickly than did those of this patient. The morphology and histology are, however, very similar.

Dr. Ingram has reviewed the literature and was reminded of a patient described by Dégos (1942), and of one of Miescher's cases. The first description of this disorder is that of Kohlmeier (1940, 1941). His case, and that of Lausecker (1949), had cutaneous and bowel necroses. Some have considered the disease to be a variant of thrombo-angiitis obliterans, and others relate it to polyarteritis nodosa. Dégos regards the disease as a separate entity and Ingram felt that his case was due to an allergic angiitis. Clinically and microscopically it is distinctive, though it may be related to thrombo-angiitis obliterans or polyarteritis nodosa.

We submit this as a case similar to that described by Dr. Ingram.

*Acknowledgment.*—We are grateful to Dr. P. J. Hare for his help with the histological studies.

REFERENCES

DÉGOS, R. (1942) *Bull. Soc. franç. Derm. Syph.*, **49,** 148, 281.
INGRAM, J. T., and SUTHERLAND, T. W. (1957) *Arch. Derm. Syph., Chicago,* **75,** 80.
KOHLMEIER, W. (1940) *Frankfurt. Z. Path.*, **54,** 413.
—— (1941) *Arch. Derm. Syph.*, **181,** 783.
LAUSECKER, H. (1949) *Acta derm.-venereol., Stockh.*, **29,** 369.

**The President** (Dr. J. T. Ingram): The case which I described has been going on for two and a half years. The only differences are that my case presents monomorphic lesions, never more than 3 to 4 mm. in size, which leave scars. The histology is very similar. My patient never shows a pustular phase and there is no tendency to confluence of lesions. It would seem clear that these are lesions dependent upon an arteriolitis.

**Pretibial Myxœdema.**—K. M. HARVEY, M.B. (for BRIAN F. RUSSELL, M.D., F.R.C.P.).

L. O., female, aged 14 years.

*History.*—First seen in January 1956, with a six weeks' history of loss of weight, increased appetite, restlessness, and swelling in neck, coincident with onset of puberty, but before catamenia. The diagnosis of thyrotoxicosis was made and treatment was begun with Neo-Mercazole with little alteration in symptoms.

In October 1956 subtotal thyroidectomy was performed—histological examination showed a parenchymatous gland with moderate histological signs of toxicity. Following this all her symptoms cleared with the exception of her exophthalmos which remained unchanged.

In January 1957, she was noticed to have firm, painless lumps over the right tibia and these were later noticed on the left leg. They have gradually increased in size and extent and have not been influenced by tri-iodothyronine by mouth (since November 1957) local hyaluronidase and hydrocortisone injections or massage.

*Investigations.*—Biopsy from leg: Pretibial myxœdema. Heavy dermal infiltration by basophilic material, strongly mucin staining.

8.8.57 and 2.12.57.—Radioiodine (thyroid) test: normal uptake.

29.11.57.—Blood cholesterol 198 mg./100 c.c.

*Comment.*—Although thyrotoxicosis may begin at any age it is uncommon in children and 80% of cases in childhood occur between 10 and 14 years of age. It is essentially similar to the same disease in adults.

Trotter and Eden (1942) in their review of 69 cases of pretibial myxœdema did not have a case below the age of 20. They stated that no case has been described in a patient without past or present thyrotoxicosis and in the majority of patients, the goitre seemed to have been of the diffuse toxic type.

REFERENCE

TROTTER, W. R., and EDEN, K. C. (1942) *Quart. J. Med.*, **35,** 229.

**Dr. G. A. Beck:** I should have thought it unfortunate that this girl had her thyroid removed before puberty when she was only 12. She now has definite exophthalmos and seems a good candidate for malignant ophthalmoplegia. I think that it was her pituitary that was at fault in the first place and that her thyrotoxicosis was only one symptom of her pituitary disorder.

The following cases were also shown:

**(1) Hyperpigmentation of Hair Following Chloroquin. (2) Incontinentia Pigmenti. (3) Poikiloderma Congenitale (Thomson).**—Dr. STEPHEN GOLD.

**Poikiloderma.**—Dr. I. J. MERENLENDER and Dr. B. SCHWARTZ.

**Linear Atrophy.**—Dr. MARY WITHAM (for Dr. W. N. GOLDSMITH).

**Scleroderma (Acrosclerosis Type).**—Dr. W. N. GOLDSMITH.

**Rosacea Treated with Intermittent Vallœstrol Therapy.**—Dr. A. JARRETT.

**Post-thrombotic Ulceration of the Toes.**—Dr. MAURICE GARRETTS (for Dr. W. N. GOLDSMITH).

**Lupus Vulgaris with Erupting Cysts.**—Dr. D. S. WILKINSON.

**Onchocerciasis.**—Dr. B. SCHWARTZ.

**Porokeratosis with Squamous Carcinoma.**—Dr. E. N. JOHNSTON and Dr. O. L. S. SCOTT.

**Eosinophilic Granuloma.**—Dr. J. SAVAGE.

**Acne Agminata. Granuloma Annulare.**—Dr. J. H. ALLISON (for Dr. F. RAY BETTLEY).

[*March* 20, 1958]

A SYMPOSIUM on **Mast Cell Disorders** was held; the opening papers were as follows:

**Urticaria Pigmentosa and Allied Disorders.**—Dr. J. MARTIN BEARE.

**Pharmacology of the Tissue Mast Cell.**—Dr. G. B. WEST.

**Cutaneous Mast Cell Tumours in the Dog, Cat and Ox.**—Mr. K. W. HEAD.

The following Cases were shown:

**Urticaria Pigmentosa in Identical Twins.**—Dr. W. FRAIN-BELL (for Dr. R. T. BRAIN).

**Bullous and Nodular Urticaria Pigmentosa.**—Dr. N. A. THORNE.

**Mastocytoma/Mast Cell Nævus in a Child Aged 4.**—Dr. M. FEIWEL and Dr. JOHN EVERALL.

**Urticaria Pigmentosa.**—Dr. G. C. WELLS (for Dr. COLIN JONES).

**Urticaria Pigmentosa with Hepatosplenomegaly.**—Dr. M. FEIWEL.

**Urticaria Pigmentosa with Attacks of Flushing.**—Dr. A. HERXHEIMER (for Dr. H. J. WALLACE).

**Urticaria Pigmentosa with Blisters.**—Dr. C. CALNAN.

**Multiple Pyogenic Granulomata.**—Dr. W. FRAIN-BELL.

DEMONSTRATIONS

**Systemic Urticaria Pigmentosa.**—Dr. C. W. H. HAVARD.

**Mast Cell Reticulosis.**—Dr. M. FEIWEL and Dr. H. HABER.

**Systemic Mast Cell Disease in Urticaria Pigmentosa.**—Dr. M. FEIWEL (for Dr. K. M. TOMLINSON).

# Section of Radiology

President—E. Duff Gray, M.A., M.D.

[*January* 17, 1958]

## Surgical Considerations in Treatment of Malignant Disease of the Thyroid Gland

By Geraldine Barry, M.S., F.R.C.S.
*The Royal Free Hospital, London*

In 1945, when Mr. C. Joll died, Mr. C. E. Shattock and I took over his Thyroid Clinic at the Royal Free Hospital and the cases which I shall discuss are, with Mr. Shattock's consent, those with which we have dealt in the past twelve years.

From a clinical viewpoint, cases of carcinoma of the thyroid fall into three groups.

I. Those which are hopelessly inoperable (9) when first seen, and we have the usual percentage of these cases in which one may try radiotherapy or $^{131}I$, resort to tracheotomy, or just the merciful dose of morphia.

II. A high percentage of cases (31) where the surgeon thinks the lesion is an innocent nodule and the pathologist reports that it is malignant, usually a papillary adenocarcinoma. This class of case is one of the best reasons I know for advising operation for a symptomless lump in the thyroid gland. There are several courses open to the surgeon: (*a*) A policy of masterly inactivity. This has been followed in a few cases and in only two has there been a local recurrence; and I do not know personally of any that has metastasized distally. (*b*) To operate again as soon as the pathological report is received, and perform a total thyroidectomy. I have done this twice only and have now abandoned the operation; after a fortnight the thyroid stump is firmly adherent to the strap muscles; the operation is troublesome and tedious, and it is difficult to identify and preserve the recurrent laryngeal nerves. (*c*) To follow the first operation by a course of deep X-ray therapy or $^{131}I$. It is still doubtful, I believe, whether one should treat a young person with a therapeutic dose of $^{131}I$; I certainly do not advise it in pre-menopausal patients except those with proved and inoperable malignancy, but there is every justification for giving the patient a post-operative course of deep X-ray therapy (and treating the resultant hypothyroidism if clinically necessary), and this is the course we generally pursue and we have had no recurrences in these cases.

III. Now we come to the group comprising the frankly malignant, probably operable cases (17). The signs and symptoms of carcinoma of the thyroid are usually easy and obvious: paralysis of a recurrent laryngeal nerve, difficulty in breathing and stridor, difficulty in swallowing from involvement of the œsophagus, a mass in the thyroid gland, unilateral to start with, hard, irregular, infiltrating, with displacement and/or compression of the trachea, and enlarged cervical nodes. Investigation includes examination of the larynx, X-ray of the trachea and chest, $^{131}I$, and biopsy, and also possibly a globulin precipitation test to exclude Hashimoto's disease. The diagnosis is not always easy; one has to differentiate a carcinoma from other types of hard goitre, e.g. Hashimoto's disease, calcified nodular goitre, calcified adenoma or cyst, or Riedel's struma: any of these conditions may simulate malignancy, especially if there is compression of the trachea and paralysis of the recurrent laryngeal nerve; from carcinomata involving the thyroid secondarily, e.g. from larynx, from apex of lung; and in those cases which present with a metastasis to trace it back to its primary focus in the thyroid gland.

In attempting to arrive at a decision as to the best course to pursue in a case of carcinoma of the thyroid, one must determine the degree of malignancy, the degree of spread in surrounding structures, and the reaction of the growth to $^{131}I$. In our series of cases we have not

found that any carcinoma has taken up $^{131}I$. We have come to rely on surgery and deep X-ray therapy, since we have found that an anaplastic undifferentiated growth which does not take up $^{131}I$ usually is sensitive to deep X-ray therapy. The size and scope of the surgical operation must be planned in the light of personal experience of the results of operation. I do not believe in large mutilating operations involving resection of larynx, trachea or œsophagus. This belief has been arrived at during the course of the past ten years, after much consultation with Dr. Phyllis Wade, the head of our Radiotherapy Department. Mr. C. Joll was always very much against doing a tracheotomy during operation because of the danger of aspiration pneumonia. Quite frequently one may find the growth adherent to the trachea or œsophagus. In my opinion it is wise to leave a small piece of growth on an intact viscus, to be dealt with by radiotherapy. I know that this statement is in direct opposition to the ordinary surgical treatment of cancer in which the growth is removed with an area of normal tissue round it.

I strongly believe in avoiding injury to both recurrent laryngeal nerves; if one is already paralysed I scrupulously safeguard the other one. Injury to both nerves means a tracheotomy and, in a high percentage of cases, death from bronchopneumonia. I think cervical nodes should be removed in a case of malignancy, but that it is not necessary to do block dissection as for carcinoma of the tongue, with removal of sternomastoid and the internal jugular veins. I believe that in every case a total or near-total thyroidectomy should be done, with clearance of lower deep cervical nodes. Any small piece of growth adherent to trachea, œsophagus, and recurrent laryngeal nerves should be left *in situ*. Dr. Wade irradiates those patients in whom I have had to leave any of the growth behind. The small volume of growth she has to destroy reduces the dosage and the reaction. The results of this form of combined surgical and radiotherapeutic treatment must be sufficiently good to justify its use, and we are getting promising results

This group consists of 17 cases which I do not think were curable by surgery alone, because at the time of operation the growth was already invading trachea, œsophagus, skin, strap muscles or recurrent laryngeal nerves. In every case I attempted a total thyroidectomy with removal of glands (but not a classical block dissection with removal of sternomastoid muscles and the internal jugular vein). The small portion of growth invading an important structure was left behind. None of these cases needed a tracheotomy and all swallowed normally after operation.

The post-operative incidence of tetany is low, but should always be watched for, closely. Cramps in the hands and feet can be relieved almost instantaneously by an intravenous injection of calcium gluconate, and thereafter the condition is treated by oral calcium gluconate, and calciferol until the calcium metabolism becomes stabilised.

As soon as the wound had healed all patients had a full course of radiotherapy, going on to the stage of moist desquamation of skin, increased hoarseness and difficulty in swallowing. After recovery from this combined treatment they have been followed up for periods of one to eight years and have been treated where necessary for myxœdema. So far we have had one death from recurrence and four deaths from other causes.

## Radiotherapy for Malignant Tumours of the Thyroid

By G. W. Blomfield, M.A., F.R.C.S., M.R.C.O.G., F.F.R.

*Sheffield National Centre for Radiotherapy and United Sheffield Hospitals*

The clinical course of a thyroid cancer depends very largely upon the pathological characteristics of the growth, and if we were to leave cases completely untreated a fair proportion would survive for ten years or so. Others would die in a matter of weeks or months. So it would be as well to consider first the clinical and pathological assessment of the disease.

From January 1, 1946, to January 1, 1955—in a nine-year period—we had some 103 cases of alleged thyroid carcinoma referred for assessment or treatment at the Sheffield National Centre for Radiotherapy. All survivors were seen and carefully re-assessed to June 1955. The notes and all the available histology of these patients were re-examined, and it was found that we had 100 consecutive cases where the diagnosis was histologically confirmed or clinically beyond reasonable doubt. This series was reported in the *Quarterly Journal of Medicine* (1957), and these have now been followed up to January 1, 1958.

Table I shows the distribution of the 100 cases. There is a 4 to 1 ratio of Female/Male

TABLE I.—THE DISTRIBUTION OF 100 CASES OF THYROID CARCINOMA BY SEX, HISTOLOGICAL CONFIRMATION, AND OTHER THYROID DISEASE

| | Total | Men | Women |
|---|---|---|---|
| Whole series | 100 | 20 | 80 |
| With histological evidence of thyroid carcinoma | 78 | 17 | 61 |
| Without histological evidence of thyroid carcinoma | 22 | 3 | 19 |
| With history of previous long-standing goitre | 18 | 2 | 16 |
| With co-existent hyperthyroidism | 7 | — | 7 |

and approximately one-fifth of the patients had a history of previous goitre. Only 22% were without histological evidence of malignancy but these mainly fell into the highly malignant category of growths, almost certainly undifferentiated for the most part.

Initial symptoms are shown in Table II. We found that swelling of the thyroid or

TABLE II.—INITIAL SYMPTOMS IN 100 CASES OF THYROID CARCINOMA

| | Without previous goitre | | With previous goitre | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| Total No. | 18 | 64 | 2 | 16 |
| Swelling of thyroid | 15 | 52 | — | — |
| Increase in size of previous goitre | — | — | 1 | 8 |
| Swelling of cervical lymph-glands | 2 | 4 | — | 1 |
| Pressure symptoms in neck | 1 | — | 1 | 3 |
| Symptoms attributable to hyperthyroidism | — | 5 | — | 2 |
| Symptoms attributable to skeletal metastases | — | 3 | — | 2 |

increased swelling in an already enlarged or goitrous gland was the commonest first symptom. Actual pressure symptoms came late and were generally of grave significance.

## PATHOLOGY

The histological types met with can be broadly divided into the following groups: (1) Papillary carcinoma. (2) Follicular carcinoma. (3) Undifferentiated carcinoma. (4) Other malignant.

We found two only in group 4 and the distribution of our cases is shown in Table III, which also indicates the five-year survival rate for the respective histological types.

It will be seen from Table III that only 19% of patients with undifferentiated growths

TABLE III.—SURVIVAL RATES OF 83 PATIENTS WITH THYROID CARCINOMA

| | Possible survivors 5 years | Actual No. surviving | Actual No. without recurrence | 5-year surv. without recurrence (rate%) |
|---|---|---|---|---|
| Whole series | 83 | 38 | 34 | 41·0 |
| With hist. evid. | 67 | 35 | 31 | 46·3 |
| Papillary | 26 | 21 | 18 | 69·2 |
| Follicular | 19 | 9 | 9 | 47·4 |
| Undiff. | 21 | 5 | 4 | 19·0 |
| Other | 1 | — | — | — |
| Without hist. evid. | 16 | 3 | 3 | 18·8 |

survived five years as compared with 69% of those with papillary growths. The papillary growths belonged to a rather younger age group. The analysis of 78 cases of thyroid carcinoma by histological type showed that the mean age for papillary carcinoma was 45, follicular carcinoma 55, and undifferentiated carcinoma 60. The average survival time for those who died was 3·1 years for papillary carcinoma, 4·8 years for follicular carcinoma and 1·3 years for undifferentiated carcinoma.

## METASTASES

We found that 59% of the patients had metastases at some time during the observed course of their disease. This is a figure which increases as we continue the follow-up. Cervical gland deposits were by far the commonest early metastases and the commonest to be observed later. Table IV indicates the number of patients with known metastases at different sites when first seen. More sites are involved as time goes on and the known secondary deposits

TABLE IV.—CASES OF THYROID CARCINOMA WITH METASTASES

| Group | No. of patients | No. with metastases present at various sites at time of diagnosis: Cervical glands | Pulmonary | Osseous | Other sites | Total No. with metastases |
|---|---|---|---|---|---|---|
| With histological evidence of malignancy .. | 78 | 17 | 2 | 4 | — | 23 |
| Without histological evidence of malignancy .. | 22 | 3 | 1 | 3 | 1 | 8 |
| Without previous goitre .. .. .. .. | 82 | 18 | 2 | 4 | 1 | 25 |
| With previous goitre .. .. .. .. | 18 | 2 | 1 | 3 | — | 6 |

develop after initial diagnosis and treatment. The histology has a very important bearing upon the progress of the disease, and secondary deposits can lie dormant for months or years.

## RESULTS IN RELATION TO TREATMENT

It will be seen from Table V that surgery combined with X-ray therapy is relatively successful, 52% surviving five years. Deep X-ray therapy alone, however, yielded a five-year survival of only 18%. Only four of these cases, however, fell among the less malignant types histologically and the remainder were either undifferentiated growths or growths from which no histology was obtained and which were most likely highly malignant tumours.

TABLE V.—TREATMENT OF 100 PATIENTS WITH THYROID CARCINOMA, CLASSIFIED BY HISTOLOGICAL TYPE OF TUMOUR

| | Surg. and deep X-ray therapy | Deep X-ray therapy | Operation | $^{131}$I | No treatment |
|---|---|---|---|---|---|
| No. of patients .. | 46 | 32 | 11 | 6 | 5 |
| 5-year survival % | 52 | 18 | — | — | — |
| Tumour type: | | | | | |
| Papillary .. | 27 | 1 | 6 | 1 | — |
| Follicular .. | 7 | 3 | 2 | 5 | 1 |
| Undifferentiated | 12 | 9 | 2 | — | — |
| No histology .. | — | 18 | — | — | 4 |
| Others .. .. | — | 1 | 1 | — | — |

Histological assessment can be difficult and the undifferentiated growths can be confused with reticulosis involving the thyroid gland (Brewer and Orr, 1953).

## TREATMENT TECHNIQUES

So much depends upon the type of case, and there are so many variations in present-day equipment ranging from the orthodox X-ray machine to kilocurie cobalt units and high energy X-ray generators, that the technicalities of treatment are peculiar to the individual case.

The chief difficulty in delivering adequate irradiation arises from two facts. Firstly the growth is generally situated in close relation to the trachea and pharynx with their limited X-ray tolerance. Secondly, extensions into the superior mediastinum cannot be reached by lateral fields. Safe dosage by external irradiation is therefore limited and extensions into the thoracic inlet form a very strong indication for using high energy or supervoltage X-rays.

## FUNCTIONING GROWTHS OF THE THYROID

Out of the 100 cases reviewed we found 7 who appeared to satisfy the criteria generally accepted for $^{131}$I therapy and all of these had one or more large doses of $^{131}$I. Two of the growths were papillary carcinomas and five were follicular. None of the undifferentiated growths took up sufficient iodine for treatment to be worth while. Six of these cases are summarized in Table VI. The first of these, a patient aged 17 with recurrent metastases in the neck, made a most remarkable recovery which could only have been due to the extraordinary concentration of the radio-iodine by the deposits. Other patients did not respond in such a spectacular manner; generally the metastases were too bulky and the sheer volume of the growths too large for the dose to be sufficient, and in some cases the concentration of iodine was good in places but bad in others where therapy consequently failed to arrest the disease.

Our most recent case (not listed in Table VI) is of interest because the secondary deposit

TABLE VI.—RESULTS OF $^{131}I$ THERAPY. THYROID CARCINOMA

| Age | Sex | Type of tumour | Clinical state | Amount given (mc.) | Result | State of patient |
|---|---|---|---|---|---|---|
| 17 | F | Papillary | Growth involving thyroid and cervical glands | 67 | Complete resolution of growth | Alive at 8 years |
| 56 | M | Follicular | Multiple bone metastases. Primary treated 10 years before | 100 | No resolution of growth | Died at 2 years |
| 59 | F | Follicular | Hyperthyroidism. Thyroidectomy revealed thyroid carcinoma | 25 | Resolution of thyroid mass. Hypothyroidism | Alive at 3 years |
| 62 | M | Follicular | Operation and X-ray therapy 12 years before. Metastases sternum, lung, liver | 90 | No resolution of growth Died of multiple metastases | Died at 9 months |
| 56 | F | Follicular | Skeletal metastases. Primary tumour thyroid | 310 | Femoral lesion responded, others remained | Died at 3 years |
| 67 | F | Follicular | Thyroidectomy and X-ray therapy 7 years before for hyperthyroidism Metastases mediastinum and lung | 93 | Regression of lung metastases Other metastases fatal | Died at 18 months |

appears to be a solitary one expanding and destroying the clavicle, and it now takes up very much more iodine after a therapeutic ablation of the thyroid gland. In fact, its uptake of iodine has risen from 1% prior to ablation to 13·5% following it. Even so, the mass is of such a size that an effective dose from $^{131}I$ cannot be expected and he is being treated by a combination of $^{131}I$ therapy and supervoltage X-rays.

My conclusion is that we can take little account of survival statistics alone in assessing the value of radiotherapy or surgery in this disease. Far more convincing than statistics is the visible disappearance of growth, and especially when that growth is causing pressure symptoms which threaten the patient's very existence. Team work between surgeon, radiotherapist and pathologist concerned with the case is of first importance, and all our resources must be brought to bear against the relentless growth once it is diagnosed. Often it will be a matter of control rather than cure.

ACKNOWLEDGMENTS

The author wishes to acknowledge the help of his colleagues, and in particular Professors D. H. Collins and G. M. Wilson, Dr. R. Kilpatrick and Dr. F. E. Neal.

REFERENCES

BREWER, D. B., and ORR, J. W. (1953) *J. Path. Bact.*, **65**, 193.
KILPATRICK, R., BLOMFIELD, G. W., NEAL F. E., and WILSON, G. M. (1957) *Quart. J. Med.*, N.S. **26**, 209.

## Radioiodine in the Treatment of Thyroid Carcinoma

By A. W. G. GOOLDEN, M.B., B.S., D.M.R.T.

*M.R.C. Radiotherapeutic Research Unit, Hammersmith Hospital, London.*

THIS summary on the use of radioiodine in the treatment of thyroid carcinoma is based on experience gained in a comparatively small group of patients with functioning thyroid metastases.

During the period 1950–1956 a total of 102 patients with thyroid carcinoma were referred to the Radiotherapy Department at Hammersmith Hospital for some form of radiotherapy. The majority were treated by external irradiation. 25 patients were given at least one therapeutic dose of radioiodine, but only 14 had metastases which were clearly shown to concentrate radioiodine.

It is convenient to consider the treatment of thyroid carcinoma from the pathological standpoint. The most satisfactory classification of malignant tumours of the thyroid is that of Warren and Meissner (1953) who distinguish three main types, papillary, follicular and anaplastic. In practice thyroid carcinomas frequently show a variety of histological patterns,

but it is helpful when discussing treatment to try to allocate a thyroid carcinoma to one of the three main groups according to the predominant histological picture. The histology of the tumours in all patients referred for radiotherapy is shown in Table I. It will be noted that

TABLE I.—HISTOLOGY OF TUMOURS IN 102 PATIENTS WITH THYROID CARCINOMA REFERRED FOR RADIOTHERAPY (1950–1956).

| | |
|---|---|
| Anaplastic .. .. .. | 32 |
| Follicular .. .. .. | 32 |
| Papillary .. .. .. | 21 |
| Reticulosarcoma .. .. | 5 |
| Squamous .. .. .. | 3 |
| Fibrosarcoma .. .. .. | 1 |
| No histology .. .. .. | 8 |
| Total | 102 |

there are rather more patients with anaplastic tumours and rather fewer with papillary tumours than might be expected in an unselected series of patients with thyroid cancer.

Radioiodine is most likely to be of use in patients with follicular carcinoma of the thyroid. It should perhaps be emphasized that it does not in any way compete with surgery as the primary method of treatment and in operable cases excision of the tumour together with the whole of the normal thyroid gland is the proper method of treatment. About half of the patients with follicular tumours already have distant metastases when first seen, and it has been noted that metastases occur most frequently in patients with well differentiated tumours. Any patient who has metastases from a follicular carcinoma of the thyroid should therefore be considered as a possible candidate for treatment with radioiodine.

It may be possible to demonstrate function in tumour tissue before the thyroid has been removed. More commonly thyroid ablation must first be carried out since normal thyroid tissue invariably concentrates iodine far more efficiently than even highly differentiated tumour tissue. Evidence of uptake of radioiodine in tumour tissue may be obtained with the thyroid still *in situ* either by external counting methods or by autoradiography. The technique of profile counting which has been described by Pochin *et al.* (1952) is a convenient method of carrying out *in vivo* studies and is particularly useful when serial measurements are made. Alternatively when the apparatus necessary for profile counting is not available localisation studies can be quite satisfactorily carried out with a Geiger or scintillation counter suitably collimated for directional scanning.

When a metastasis is accessible to drill or needle biopsy or a lymph node can be excised, a specimen of tumour tissue may be obtained after giving a tracer dose of radioiodine and examined both for its histology and by autoradiography. This is undoubtedly the most sensitive and discriminating method of detecting uptake of radioiodine in tumour tissue.

Although thyroid tumours may concentrate iodine while the thyroid gland is still *in situ*, metastases cannot be effectively treated with radioiodine until the thyroid has first been ablated. Surgical ablation is the method of choice but when the primary tumour is considered to be locally inoperable or the general condition of the patient is poor the thyroid may be destroyed by radioiodine; a dose of 50–100 millicuries is usually sufficient. In general, patients most likely to be suitable for treatment with radioiodine are those with metastases from well-differentiated follicular carcinoma of the thyroid. Although the histological appearance of the primary tumour gives the best indication of whether the metastases are likely to function or not, the functional behaviour of thyroid tumours cannot always be related to their structure. In this series of patients with functioning metastases, two had papillary carcinomas of the thyroid; another who had a poorly differentiated primary adenocarcinoma of the thyroid developed a secondary deposit in the pelvis which was well differentiated and concentrated iodine. This is contrary to the usual behaviour of metastases which tend to be less differentiated than the parent tumour. The remaining patients all had differentiated follicular carcinomas which were forming colloid. In one instance a rib metastasis was so well differentiated that it was impossible on histological grounds to distinguish it from normal thyroid tissue, an example of what used to be called "benign metastasizing struma". On the other hand, in several patients with differentiated follicular carcinoma it proved impossible to promote any uptake in metastatic tissue even after thyroid ablation and the induction of myxœdema. From the foregoing it will be apparent that the selection of patients for treatment with radioiodine is not easy, since it is impossible to predict with any degree of certainty whether or not thyroid ablation is likely to have the desired effect of inducing uptake in metastatic tissue. It is, however, extremely unlikely that anaplastic tumours will respond to treatment with radioiodine and when skeletal deposits from this type of tumour give rise to symptoms they are best treated by external irradiation.

21 patients with metastases were selected for treatment with radioiodine. Before thyroidectomy evidence of uptake in tumour tissue was obtained in 9 patients. After thyroid ablation a further 5 patients were shown to have functioning tumours, but in the remaining 7 patients no uptake could be demonstrated in metastatic tissue. After thyroid ablation the patients are allowed to become myxœdematous. The signs and symptoms of myxœdema begin to appear about six to eight weeks after operation and further tests for radioiodine uptake may be made at about this time. There may at this stage be sufficient uptake to warrant giving a therapeutic dose or alternatively it may be possible to enhance uptake either by giving an antithyroid drug or by the injection of thyrotrophic hormone (T.S.H.). Both methods have certain advantages.

Both growth and function in functioning thyroid carcinomas can be modified by the action of T.S.H. Thus a high blood level of T.S.H. will increase the rate of accumulation of iodine by tumour tissue. Conversely if the secretion of T.S.H. by the pituitary is inhibited by the administration of thyroid hormone, iodine uptake may be abolished and restraint of growth or even regression may occur. The blood level of T.S.H. may be raised either by the injection of exogenous T.S.H. or by inducing myxœdema and thus stimulating the pituitary to increase the output of endogenous T.S.H. If a patient becomes grossly myxœdematous following thyroid ablation it is unlikely that any useful purpose is served by giving an antithyroid drug. If on the other hand metastatic tissue is producing sufficient hormone to maintain the patient in a nearly euthyroid or only slightly hypothyroid condition then the tumour will not be subjected to the maximum stimulation by T.S.H. and an antithyroid drug given for a period of a month or so is likely to increase further the uptake of radioiodine and ensure the optimum utilization of a therapeutic dose. Most of our patients had tumours which were physiologically efficient and in these circumstances an antithyroid drug has usually been given with distinct advantage. One disadvantage of using an antithyroid drug to increase uptake is that growth of the tumour is also stimulated and where, for example, a deposit is already causing compression of a nerve or nerve root, further prolonged stimulation of growth may be strongly contra-indicated. In circumstances such as this it may be preferable as an alternative to stimulate uptake by the injection of T.S.H. One or several intramuscular injections may be given. The maximum effect on the uptake of radioiodine will occur twenty-four hours after the last injection. It might seem that the injection of non-physiological doses of T.S.H. would be preferable to the use of an antithyroid drug for increasing uptake in tumour tissue. It does not involve the delay in treatment that is inevitable when an antithyroid drug is used and it obviates the need for making the patient myxœdematous. It would of course be extremely difficult to make a valid comparison of the two methods but in practice T.S.H. seems to be the less reliable of the two.

Dosage in radioiodine therapy is quite empirical. Our usual practice is to give a dose of 150–200 mc. Symptoms of radiation sickness may develop after doses of this order but they are usually quite mild. Further treatment is given at intervals of three to four months so long as any uptake of radioiodine by tumour tissue remains. Two or three doses have usually been required but in no case has the total cumulative dose exceeded 600 mc. It has been found that progressively smaller amounts of radioiodine are concentrated by tumour tissue after each therapeutic dose.

Patients who have been treated with radioiodine should always be maintained on a full replacement dose of thyroid hormone both in the intervals between treatment and after their treatment is completed. It is probably best to aim at the highest dose which can be tolerated without producing any symptoms of thyroid intoxication and it must be emphasized that this is an important part of the treatment of patients with thyroid carcinoma. Balme (1954) described regression of secondary deposits in the lungs in a patient with a thyroid carcinoma who was treated with thyroxine. The management of patients who are undergoing treatment with radioiodine is greatly facilitated and the periods of disability due to hypothyroidism are reduced if triiodothyronine is used instead of thyroxine for maintenance therapy. When patients are maintained on thyroxine it has to be stopped about a month before radioiodine tests are carried out. With triiodothyronine which has a rapid metabolic effect and a shorter duration of action than thyroxine it is only necessary to wait about two weeks before carrying out radioiodine tests. Triiodothyronine may be started again twenty-four hours after a therapeutic dose with rapid relief of the myxœdematous state.

There are two serious complications which may rarely occur after radioiodine therapy, namely radiation damage to the lungs and radiation damage to the bone-marrow. The occurrence of radiation pneumonitis and fibrosis following radioiodine was reported recently by Hall *et al.* (1957). They noted this complication only in patients with multiple or diffuse metastatic involvement of the lungs. One of our patients with multiple deposits in the lungs was given three therapeutic doses of radioiodine, receiving in all 450 mc. She died two years later from cor pulmonale and at autopsy was found to have marked pulmonary fibrosis; it is probable that this was attributable to radiation.

Therapeutic doses of 150–200 mc. usually have a slight temporary effect on the peripheral blood count producing a fall in the number of circulating platelets and lymphocytes and the polymorphonuclear leucocytes may also be affected. More severe changes are liable to occur in patients who have multiple deposits in bone, and persistent leucopenia which may be of sufficient severity to interfere with further treatment may occur. We have had one case of severe bone-marrow depression after a single therapeutic dose. The patient who was thyrotoxic when first seen had pulmonary and skeletal metastases. When the thyrotoxicosis had been controlled with carbimazole a total thyroidectomy was performed. Carbimazole was continued for a few weeks post-operatively and a therapeutic dose of 200 mc. of radioiodine was then given. Initially his general condition improved remarkably and pain which had previously been severe was relieved, but four weeks later his condition suddenly deteriorated and he developed petechiæ and spontaneous hæmorrhages. Examination of the bone-marrow showed almost complete aplasia. The effect of radioiodine on the peripheral blood count is shown in Fig. 1.

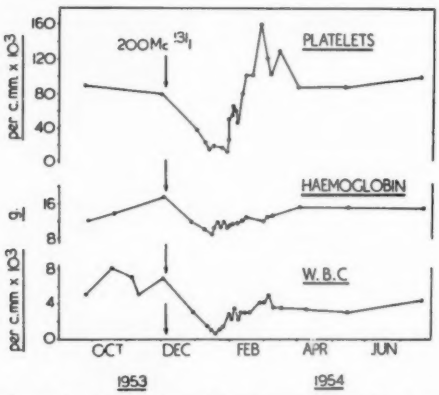



FIG. 1.—The change in the peripheral blood count following a single therapeutic dose of 200 mc. of $^{131}I$.

He recovered from this episode but later the metastases became active and he again became thyrotoxic. He was eventually found at autopsy to have extensive skeletal deposits. Carcinoma of the thyroid is sometimes found in association with thyrotoxicosis but it is most unusual for metastatic tissue to cause hyperthyroidism; for this to occur a relatively enormous amount of neoplastic tissue must be present.

Firm conclusions cannot be drawn on the results of treatment from such a small series as this, especially when the natural history of the disease is so variable. 2 patients with skeletal metastases have survived for more than five years; another with multiple pulmonary deposits died seven years after treatment. On the other hand some patients who were in a very poor condition and had multiple metastases when first seen did not survive for more than a few months.

It may be asked whether radioiodine can be considered as a curative form of treatment. It would seem that in patients who have a limited number of metastases radical treatment should be given and an attempt made to eradicate the disease. Even if this is not successful, at the least very long-term palliation can be achieved.

## REFERENCES

BALME, H. W. (1954) *Lancet*, i, 812.

POCHIN, E. E., MYANT, N. B., HILTON, G., HONOUR, A. J., and CORBETT, B. D. (1952) *Brit. med. J.*, ii, 1115.

RALL, J. E., ALPERS, J. B., LEWALLEN, C. G., SONENBERG, M., BERMAN, M., and RAWSON, R. W. (1957) *J. clin. Endocrin.*, **17**, 1263.

WARREN, S., and MEISSNER, W. A. (1953) Atlas of Tumour Pathology. Washington; Sect. IV, fasc. 14.

# Section of Neurology

President—W. Ritchie Russell, C.B.E., M.D., D.Sc., F.R.C.P.

[*January* 2, 1958]

## Chronic Benign Trigeminal Paresis

By Professor Brodie Hughes, F.R.C.S.
*Birmingham*

Cases in which disease has presented as a trigeminal paresis are not common and those in which disease seems to remain in that single nerve must be quite rare. It is with the latter group that I am concerned here.

There are a variety of conditions in which trigeminal pain, paræsthesiæ and paresis may form the presenting picture. In our neurosurgical records most of these have been tumours or aneurysms though we have one example of syphilis and one case of disseminated sclerosis in the group. Aneurysms have not been common in the group and in most instances of intra-cavernous carotid sacs the clinical picture has been contaminated early by oculomotor pareses and the diagnosis not been in doubt.

It might be expected that neurinomata of the V nerve would loom large in this small collection but this has not been our experience and Olive and Svien (1957) have confirmed this. They found in several instances that quite large tumours could be present on the fifth root or ganglion without any symptoms or signs referable to the nerve. In our series meningiomas have been by far the most common tumours to cause this picture. In one instance pain and paræsthesiæ, later followed by sensory deficit, were present for five years before other signs appeared. This was a middle fossa tumour. In another instance symptoms were noted nineteen months before other signs appeared in a posterior fossa meningioma.

One patient we had, travelled to Belfast in the course of his work and could not close the porthole by his bunk. He awoke in the morning with a stiff face, which he attributed to the draught, and later this became painful and sensory and motor impairment appeared. Investigated two months later his only signs were in the V nerve. He proved to have a metastasis in the skull base from a bronchial carcinoma and we have found that this is a not uncommon sort of story in such cases. Nasopharyngeal carcinoma spreading up through the foramen ovale may produce a similar motor and sensory trigeminal paresis.

I shall now turn to the story of 3 cases in which trigeminal sensory paresis appeared, progressed slowly and appeared to have a quite benign significance. The individual case histories are so similar that I shall not need to detail them. All were adults—33, 49 and 64 years of age; there were 2 women and 1 man. The onset of symptoms was sudden. The male patient was awakened in the middle of one night with a severe pain in the left cheek. This was sharp and occasionally burning. Teeth were extracted without relief and the severe pain lasted for three or four days. Thereafter he experienced a dull aching pain with occasional stabs and burning sensations. Within a few weeks he noticed an area of numbness in the cheek and over a period of twelve years this numbness, and the pain gradually spread to cover the whole trigeminal distribution. In a second patient an almost identical story had been elicited and the history dated back six years. In the third patient only eleven months had passed since the onset and she complained rather more of paræsthesiæ than of pain. (I am indebted to Mr. J. M. Small, under whose care she was, for the details of this case which I also examined personally.)

In 2 of the cases, examination did not disclose any abnormality other than in the V nerve.

Motor function was unimpaired. Sensory loss was present over most of the trigeminal distribution densest in the area where it had first appeared and less marked elsewhere; both touch and pain sensibility were affected. We did not feel that the pattern of sensory loss was such as to suggest any especial location for the disorder. There was no evidence of sympathetic or parasympathetic dysfunction. In the third case the trigeminal findings were the same. Three years before she had developed quite suddenly a facial paralysis on the same side in which partial recovery had taken place. This was assumed to be an ordinary Bell's palsy but may, for all we know, have had the same ætiology as the trigeminal paresis.

They were all, of course, presumed to have some tumour involving the V nerve, probably in the brain-stem or posterior fossa in view of the motor sparing. All routine investigations were negative, however, and operations were undertaken with the primary purpose of dividing the trigeminal sensory root to relieve pain and paræsthesiæ. The gasserian ganglion and the whole length of the sensory root to its entry into the pons were exposed by a subtemporal approach splitting the tentorium. The findings in all the cases were essentially the same. The sensory root appeared to be reduced to a few wisps of nerve fibre. These were embedded in considerably thickened arachnoid which extended to the side of the pons. No other abnormality was seen in the brain-stem itself, in other cranial nerves in the posterior fossa or elsewhere within the limits of the exposure. The remaining fibres of the sensory root were divided. In two instances this resulted in complete relief of pain and paræsthesiæ; in the third instance some burning causalgic-like pain persisted. Histological examination of the material removed, which included the sensory root, ganglion and arachnoid, showed degenerative changes in the fibres remaining. There were collections of lymphocytes associated with degenerating fibres and the ganglion cells also showed degenerative changes with satellitosis. There was a marked increase of fibrous tissue showing hyaline changes. Our neuropathologist, Dr. Walter Smith, remarked in one report "has this nerve been injected?" It had not.

The nature of these cases remains, to me, quite mysterious. Search of the literature has not resulted in my finding anything very helpful, though cases of a somewhat similar type have been recorded. Dr. Wilfred Harris reported in 1935 3 cases of sudden sensory loss in the face. This was followed by recovery in a period varying from six weeks to four years. As the anæsthesia wore off pain characteristic of tic appeared and necessitated injection treatment. He also mentions in the same report three similar cases in which the anæsthesia recovered but no pain appeared. These do not really seem similar to my cases in many respects. The only other report I can find was that of Dr. Rowland Hill in 1954. His first case showed features somewhat different to mine. Pain was not present but paræsthesiæ marked and there was an additional mild motor paresis. His second case was rather like that of Dr. Harris and developed a mild motor and sensory paresis which recovered in part within a week. Dr. Hill noted at that time that he had seen 12 such cases and stressed that some degree of recovery was usual, that peripheral sympathetic and parasympathetic paresis was common and that paræsthesiæ were the rule rather than pain. He considered it to be a peripheral neuropathy probably distal to the ciliary ganglion.

In November last Dr. J. D. Spillane (1957) presented some material on the same subject to the Association of British Neurologists. He has very kindly sent me some notes on his own 10 cases of motor and sensory paresis, some of them bilateral. He also stressed the tendency to recovery and was particularly interested in trophic phenomena resulting in ulceration of the nose.

I have 2 further cases which probably fall into this group. Both were women, both developed a sensory trigeminal paresis on one side rather rapidly. There was no motor involvement. In both, skull X-rays were thought to show decalcification in the skull base around the appropriate foramen ovale and they were labelled metastases or local spread of cryptic carcinoma of the pharynx; one received X-ray therapy. They have been followed-up for four and nine years respectively without developing any signs of pharyngeal or other growth. The sensory paresis has progressed to completion but no other signs have appeared.

Thus opinions on the location of the disease have varied from the extreme periphery to the brain-stem. So far as I am aware mine is the first pathological material to be produced from these cases and this merely shows a chronic fibrous tissue reaction around degenerating nerve fibres with some lymphocytic infiltration.

I would suspect that we are dealing here with a mixed bag of disorders. It would seem likely that those cases with acute onset and rapid recovery, which form the majority of the small number reported, may well be some form of acute neuropathy. Some indeed may be minor brain-stem thromboses as was suggested, I think, by Dr. Wilfred Harris. The clinical findings in some of Dr. Rowland Hill's cases suggest strongly that the lesion was quite peripheral.

My own group would seem to be a little different and one could include Case 1 of Dr. Hill and several of Dr. Spillane's cases in the same group. The condition would seem to be some mild chronic inflammatory process judging by the histology, probably to be located in the ganglion or sensory root itself and leaving the motor root intact. The sporadic appearance of mild motor paresis in the group seems to be quite puzzling. We had thought in our series that the absence of motor involvement constituted a convenient label whereby we could exclude local involvement as by tumour, and this may well be so. On the reverse side, however, its presence does not indicate such a lesion for several of the cases reported have shown just such a paretic pattern. That the condition could be caused by the arachnoiditis itself must also be considered though I would feel, as in most of such controversies, that the arachnoidal reaction was a secondary process. I cannot do better than to label it chronic benign trigeminal paresis.

REFERENCES

HARRIS, W. (1935) *Brit. med. J.*, i, 1112.
HILL, T. R. (1954) *Proc. R. Soc. Med.*, **47**, 914.
OLIVE, I., and SVIEN, J. H. (1957) *J. Neurosurg.*, **14**, 484.
SPILLANE, J. D. (1957) Personal communication.

## The Central Control of Sensory Inflow

By G. D. DAWSON, M.Sc., M.B., Ch.B.
*Department of Physiology, University College London*[1]

*Historical Background*

WHEN we stimulate a patient somewhere in the periphery the central effect may be judged in two chief ways. We can ask the subject to tell us if he can feel anything, and if so to describe to us the quality of his sensations; or in some cases we can make electrical records from the scalp of events following the arrival of the afferent volley in the sensory area. Neither method gives any direct evidence about how the volley of nerve impulses may have been modified on its way from the periphery to the cortex. If the lower levels of the afferent pathway are not diseased it is very tempting to assume that the incoming volley arrives at the cortex relatively unaltered. Any changes in the responses to stimulation, subjective or objective, can then be interpreted in terms of the state of the cortex. Head and Holmes (1911) took the view that this assumption was incorrect. They argued, from the evidence of the sensory release phenomena produced by certain lesions of the lateral parts of the thalamus, that the afferent impulses had to "pay toll" on their way from the periphery to the cortex. The mechanism of this sensory release they explained in terms of destruction of the endings or connexions of the cortico-thalamic fibres described by Cajal (1909). Through these fibres they supposed that the cortex normally exerted an inhibitory influence on the thalamus and they considered the possibility that similar inhibitory influences might be active at lower levels in the sensory pathway. However they dismissed the evidence, apart from that derived from thalamic lesions, as unsatisfactory. Until comparatively recently these ideas seem to have been largely neglected. This may have occurred in part because the development of electrical recording methods led to a concentration of interest on the mapping of the cortical sensory receiving areas in animals. If the anæsthesia is deepened the only potentials then seen following the stimulus are stereotyped and can be attributed to the arrival of the afferent volley at the cortex; nothing clearly due to the discharge of cortical neurones is found and there is no spontaneous activity. In this case transmission at the synapses in the pathway below cortex is continuing when the cortex itself is failing to respond. From this it seems to have been inferred that if the cortex is working normally conditions are unlikely to be such that an afferent volley will be reduced in size or blocked at subcortical synapses. However, Adrian (1954) has pointed out that it is more difficult to record the cortical potentials due to stimulation when the anæsthesia is light than when it is deeper. This led him to suggest that the deep anæsthesia might have suppressed "an inhibitory activity which would check some or all of the signals at a lower level if it were operative". Fresh evidence about this possibility has become available over the last few years, largely from the work of Hagbarth and Hernández-Péon and their collaborators, and it is chiefly this that I want to consider.

[1] On leave from the M.R.C. Neurological Research Unit, The National Hospital, Queen Square, London.

*Personal Observations*

My own interest in the problem of the modification of sensory inflow arises from observations made on certain patients subject to myoclonic seizures. In these people a sensory stimulus applied to the periphery leads to an electrical response, recordable from the scalp over the sensory area, which is many times larger than that found in healthy people (Dawson 1947*a*, 1947*b*). These responses, like those in healthy people, were largest over the sensory area appropriate to the part stimulated and had a short latency, about 20 to 25 milliseconds when the stimulus was applied to the wrist. The records therefore probably represent the events in sensory cortex at the time of arrival of the afferent volley, or soon after this, and they are quite distinct from the responses to startling stimuli or "K complexes" which have a longer latency and are largest near the vertex, irrespective of the site of stimulation. The increased size of the electrical responses in these people in whom sensory stimulation provokes myoclonus at once gives rise to a problem. Is the increase due to an abnormal response of the cortex to an incoming volley of normal size, or is the incoming volley itself increased? The possibility that the great difference in size between the responses in the healthy and myoclonic subjects might be due to a subcortical mechanism was considered (Dawson loc. cit.), but as yet all it has been possible to settle, using the methods described elsewhere (Dawson, 1950), is that the afferent volley in the peripheral nerve stimulated is not abnormal in size. Clearly before going further in interpreting these scalp records it was necessary to get more evidence about the constancy or otherwise of the afferent volley when it reached the cortex. For this reason some investigations on animals were begun in the Physiology Department at University College.

A variety of drugs, notably chloralose, will produce acutely a state in which the animals to which they are administered jerk freely to slight sensory stimuli. This state is closely analogous to the stimulus-sensitive myoclonus found in man. Ultimately this analogy may break down but in the meantime it remains sufficiently close to encourage further investigation. A less severe form of the same state occurs at some levels of anæsthesia with trichlorethylene and the rats used in these experiments have been anæsthetized with this drug. Records from the exposed primary somatic sensory cortex, which is easily accessible in the rat, show that peripheral stimuli produce potentials there which are in many respects closely similar to those which may be recorded from the scalp in myoclonic man. When the stimulating conditions are altered many of the same changes appear in the responses as are seen to occur in man. To find how far these changes may be associated with changes in the afferent volley at lower levels, simultaneous records have been made from cortex and from a needle electrode in the cuneate nucleus or dorsal column. These records strongly suggest that at some levels of anæsthesia the afferent volley may be considerably modified even at the first sensory synapse. It has been found that the discharge in post-synaptic elements of the cuneate nucleus, produced by a single stimulus to a forepaw, can be reduced 50% by a preceding stimulation of the primary sensory cortex. These observations need to be repeated and extended and the snags in interpreting them are only too evident, but it is clear that no reliance can be placed on the arrival at the cortex of an unaltered afferent volley. Any evidence of similar effects elsewhere, and of how they may be produced, must clearly be taken into account.

*Evidence Gained from Experimental Work on Animals*

The posterior column nuclei do not seem to have been extensively studied. The work of Terman (1941) showed that the volleys of impulses coming up the column of Burdach were passed through the cuneate nucleus with little or no alteration, which led him to conclude that the nucleus was a simple relay. However the animals he used were either deeply anæsthetized or decerebrate, both conditions which could have removed any descending influence on the nucleus. Amassian (1950) confirmed Terman's findings and concluded that under the anæsthesia he was using interaction between two volleys produced by peripheral stimuli was slight at or below the level of the cuneate or gracile nuclei. He did however show clearly that a preceding stimulus to part of the sensory cortex, under light Dial anæsthesia, could partially block the response of other parts of the sensory cortex to stimulation of a peripheral nerve. This blocking he considered was occurring at the level of the thalamus. Later Amassian and De Vito (1954) showed that blocking might occur in the cuneate nucleus if a second stimulus followed a first by a short interval, but the degree of the blockage seemed to be related more to the closeness of the stimuli than to any descending controlling influence. Adey, Segundo and Livingstone (1954) studied the effect of cortical stimulation on the conduction of volleys through the brain-stem and showed that it could be either increased or reduced. However it is not clear what were the structures involved, but it seems that they were not the specific afferent pathways. A short report by Scherrer and Hernández-Péon (1955) suggests a different picture. They report that in curarized

unanæsthetized cats, the response in post synaptic elements of the gracilis nucleus after a single stimulus to the posterior columns at a lower level, could be greatly depressed or abolished by stimulation at the same time of the sensory cortex or the reticular formation of the brain-stem. Here we may note that Walberg (1957), working in Brodal's laboratory, has recently shown that ablation of various parts of the sensory cortex produces degeneration of fibres terminating in the cuneate nucleus on either side. It therefore seems likely that there are pathways descending from the cortex to the posterior column nuclei without any synaptic interruption in the brain-stem.

One of the most important contributions to this subject is probably the paper by Hagbarth and Kerr (1954). These authors, who also studied the centrifugal fibre systems in the olfactory pathway (Kerr and Hagbarth, 1955), found that the volley ascending the ventral columns following a stimulus to a posterior root, could be reduced below the level of detectability by simultaneous stimulation of sensory cortex, cerebellum, or brain-stem reticular formation. A similar reduction of post-synaptic activity was found in the trigeminal sensory nucleus by Hernández-Péon and Hagbarth (1955) when they stimulated cortex and elsewhere. Here again an anatomical basis for the effect has been shown by Brodal, *et al.* (1956) who have described degeneration of fibres in various parts of the sensory trigeminal nucleus following cortical ablations. In all these experiments the authors stress two points. First, that the effects produced by the conditioning stimuli were always reductions or depressions of the afferent volleys. They concluded that the normal state was for the afferent inflow to be checked constantly by a tonic activity descending from cortex, cerebellum or brain-stem. Secondly they emphasized that this controlling mechanism is very sensitive to anæsthesia and is one of the first functions to fail as it is deepened. This last finding may account for the failure of earlier workers to detect these effects.

It is natural to ask how these alterations in the afferent volley at the first sensory synapse fit in with the normal behaviour of the intact animal. The evidence here comes largely from the work of Hernández-Péon *et al.* (1957) who examined the effect on the specific sensory responses of changing attention. With electrodes implanted in the visual and auditory areas in cats, and also in various subcortical situations, they were able to study the cortical responses to one or more stimuli whilst the cats were unanæsthetized and unrestrained. The results show that the responses to a flashing light recorded from the occipital cortex were almost abolished when the animal was given fish to smell. At the same time as this reduction was found in the cortical responses these authors state that the afferent volleys in the optic tract and at higher levels in the optic pathway, were reduced as well. The reduction of cortical activity is therefore apparently in part at least due to a reduction of afferent inflow. Their work also suggests that if an auditory stimulus is repeated until it has lost any significance for the animal, the diminution which is then seen in the response of the auditory cortex is associated with a reduced afferent inflow.

*Responses in Man*

We may well here turn our attention to man again. One of the most notable features of the cortical responses to sensory stimulation, and I refer now to the responses of the specific sensory areas which have a short and relatively constant latency, is their great variability in size and form. When it was assumed that the afferent volley arriving at the cortex was relatively constant in size, this variability of the responses was attributed to changes in the state of the cortex associated with its spontaneous activity; the size of the response was thought to depend on the events in cortex at, or shortly before the arrival of the afferent volley. Such effects may indeed occur, it will not be easy to exclude them, but it is clear that alterations in the size of the afferent volley may be of at least equal importance. So far as the responses in man to somatic stimuli are concerned no factors clearly correlated with the variations in their size have yet been found. This may be due to the difficulty of concentrating attention on a somatic stimulus for several minutes continuously. To record the responses in a healthy person it is usually necessary to average or integrate 100 or more responses and the rate of stimulation can rarely be faster than once or twice a second (Dawson, 1954). However during some work with Dr. W. A. Cobb on the responses in the occipital regions to bright flashes of light, it was found that these responses could be modified in a repeatable way by direction of the subject's attention. When he gazed into a blank field the second, negative going, phase of the response remained small; but when his attention was concentrated on a small red light in the middle of the field this second phase of the response was considerably enlarged and the first, positive going, phase probably shortened. When attention was distracted from the visual field, as for example when someone came into the laboratory and began talking, it appeared that the occipital responses to the flashes were reduced in size. No satisfactory records of this last effect were obtained as the responses were being recorded and averaged over a period of some minutes; apparently the interest of the conversation was not sufficient to keep the subject's attention for the

whole of this time. I believe that Dr. M. Jouvet of Lyons has had the opportunity at operation of examining in man the potentials in the optic radiation following a flash of light in the eye. He found that the direction of attention altered the afferent volley in the optic pathway, subcortically, so it seems fair to ascribe a good part of the changes in the responses I have recorded through the skull to changes in the afferent inflow to the cortex.

Further evidence about the regulation of afferent inflow to the cortex in man comes from the work of Hagbarth and Höjeberg (1957) who made records during an operation from electrodes in the white matter below the sensory cortex. They showed that the afferent discharge to the hand area of the cortex was greatly increased when the depth of the barbiturate anæsthesia was increased. This appears to confirm the finding in animals that the tonic inhibitory influences acting on sensory synaptic transmission are reduced even by light anæsthesia. In unanæsthetized subjects they were unable to detect any afferent discharge to the cortex with the methods then available, so they were unable to examine the effects of distraction of attention. These observations are of some interest in connection with routine EEG examination where there has for some time been an apparent conflict of ideas. On the one hand it has seemed that abnormalities could best be evoked from the record by stimulating the patient with a flashing light or sudden noises; on the other if the patient is left quiet and put to sleep with a sedative this also has seemed to be effective. If one of the first effects of barbiturate hypnosis is to increase the afferent inflow to cortex, and its depressant effect can be kept minimal, these two approaches to evoking latent abnormalities in the EEG may not be so divergent as has sometimes appeared. Clearly the effects in man of light anæsthesia or sedation on the cortical evoked potentials will repay further study.

If we accept the idea that there is a continual descending influence checking the afferent inflow to cortex, and that the withdrawal of this control may be the cause of the increase in size of the cortical responses to sensory stimuli in some kinds of myoclonus, does this give us any help in deciding where the lesion or abnormality may be in these cases? Probably not, because the evidence from animal experiments suggests that the controlling effect may be produced by activity in cortex, cerebellum or brain-stem. This itself is of some interest because of the many sites which have been incriminated and in which pathological conditions have been found when myoclonus has been a symptom.

In the cases of Dr. E. A. Carmichael's that I have had the opportunity of examining Dr. Greenfield felt that the cerebellar abnormalities were probably the dominant ones. On the other hand Watson and Denny-Brown (1953) emphasize that they consider a diffuse cortical pathology to be a necessary condition for the occurrence of myoclonus. Here we can recall that Head and Holmes felt that the reason release like that of the thalamic syndrome did not occur with localized cortical lesions was probably that the cortico-thalamic fibres had a widespread origin; it was therefore unlikely that the release would occur unless the cortical lesion also was widespread. Others have described lesions in the brain-stem and the cerebellar peduncles. Any of these findings might be compatible with the idea that the excessive cortical discharges in myoclonus are due to a failure of the normal restraining influence on the afferent inflow to the cortex. None of them need occasion surprise until more precise knowledge is available about the pathways involved and their characters.

## Conclusion

One can hardly leave the subject of the control of sensory inflow without some speculation about the states of hypnotic and hysterical anæsthesia. It has perhaps been natural to look on these conditions as being concerned only with the very highest levels of activity in the nervous system. But it now seems that while the actual inititation of a switch of attention may occur at a high level, the process of reducing the inflow in one modality, or in some part of that modality, and of increasing the inflow through another modality, is perhaps carried out at almost the lowest level in the afferent pathway. The possibility then arises that in a state of hypnotic anæsthesia the afferent inflow may be reduced or blocked at the first sensory synapse. Although some information is available about the effect of hysterical anæsthesia on the blocking of the alpha rhythm in the EEG by tactile and other stimuli (Titeca, 1940) there does not seem to be any information about the effect on the evoked potentials in the primary sensory areas. This would clearly be of considerable interest as an indication of the level at which sensory block, if any, occurs in these conditions.

For some time we have had available the ideas which were implicit throughout Head and Holmes' paper, and which were explicit in several places in it. We now have physiological evidence of the existence of these mechanisms for the control of sensory inflow in animals, perhaps in man also. It therefore seems that in studying alterations of sensibility, or the central physical effects of stimulation, the effects on the afferent impulses of lesions remote from the direct sensory pathway must be considered and possible gross alterations in the size of the afferent volley reaching the cortex must be allowed for.

REFERENCES

ADRIAN, E. D. (1954) In: Brain Mechanisms and Consciousness. Edited by Adrian, E.D. Bremer, F., and Jasper, H. H. Oxford; p. 237.
ADEY, W. R., SEGUNDO, J. P., and LIVINGSTONE, R. B. (1954) *Amer. J. Physiol.*, **179,** 613.
AMASSIAN, V. E. (1950) *Res. Publ. Ass. nerv. ment. Dis.*, **30,** 371.
——, and DE VITO, L. L. (1954) *Amer. J. Physiol.*, **179,** 615.
BRODAL, A., SZABO, T., and TORVIK, A. (1956) *J. comp. Neurol.*, **106,** 527.
DAWSON, G. D. (1947*a*) *J. Neurol. Psychiat.*, **10,** 134.
—— (1947*b*) *J. Neurol. Psychiat.*, **10,** 141.
—— (1950) *Brit. med. Bull.*, **6,** 326.
—— (1954) *Electroenceph. clin. Neurophysiol.*, **6,** 65.
HAGBARTH, K.-E., and KERR, D. I. B. (1954) *J. Neurophysiol.*, **17,** 295.
——, and HÖJEBERG, S. (1957) *Nature, Lond.*, **179,** 526.
HEAD, H., and HOLMES, G. (1911) *Brain*, **34,** 102.
HERNÁNDEZ-PÉON, R., and HAGBARTH, K.-E. (1955) *J. Neurophysiol.*, **18,** 44.
——, GUZMÁN-FLORES, C., ALCARAZ, M., and FERNÁNDEZ-GUARDIOLA, A. (1957) *Acta Neurol. Latinoamer*, **3,** 1.
KERR, D. I. B., and HAGBARTH, K.-E. (1955) *J. Neurophysiol.*, **18,** 362.
RAMÓN y CAJAL, S. (1909) Histologie du Système nerveux. French trans. by Azoulay. Paris.
SCHERRER, H., and HERNÁNDEZ-PÉON, R. (1955) *Fed. Proc.*, **14,** 132.
TERMAN, P. O. (1941) *J. Neurophysiol.*, **4,** 153.
TITECA, J. (1940) *Mém. Acad. R. Méd. belg.*, Collection in–8°, Ser. 11, **1,** fasc. 5.
WALBERG, F. (1957) *Brain*, **80,** 273.
WATSON, C. W., and DENNY-BROWN, D. (1953) *Arch. Neurol. Psychiat., Chicago*, **70,** 151.

## A Form of Subacute Encephalopathy of Uncertain Ætiology

By S. NEVIN, M.D., F.R.C.P., and W. H. MCMENEMEY, M.D., F.R.C.P.
*London*

IN this paper we wish to discuss a subacute form of encephalopathy which has been rediscovered in recent years, and which though possibly rare, has many features of interest, both clinical and pathological. It has no accepted designation, the nature of the disease not being established and it has therefore been described in the literature under different titles.

Spielmeyer (1922) illustrated the condition and referred to it as a peculiar disease process of late adult life. He made use of it in order to exemplify status spongiosus, by which he meant a softening of the nervous tissue (as distinct from the usual ischæmic softening) resulting from a failure of the glia to fill the cavities in the tissue.

In 1930 Hallervorden, under the heading of "peculiar and non-classifiable conditions", gave a short but good account of the case from which Spielmeyer had taken his illustration. As well as the status spongiosus and glial proliferation pictured by Spielmeyer, Hallervorden described a loss of nerve cells with the residual nerve cells exhibiting severe changes (in the sense of Nissl) and cell shrinkage, the former affected mainly the larger, and the latter the smaller nerve cells. The whole cerebral cortex was involved, but especially the posterior parts: Hallervorden, in fact, described the occipital grey matter as being so filled with glial cells that everything else seemed embedded in the protoplasmic mass of their cell bodies. The patient was a 60-year-old woman and the duration of her illness was three months. It was characterised by progressive mental deterioration and focal symptoms referable to the left temporo-occipital region. The onset was possibly gradual; she became silly, perverse and forgetful and was anxious and unable to express herself properly or find her own room. In the clinic she tottered as she walked, tended to hold her arms outstretched or to make flinging movements with them. A right hemianopia, alexia, nominal aphasia, spatial disorientation and apraxia could all be demonstrated before severe mental deterioration set in with perseveration, senseless speech and much excitement. She died from erysipelas. Hallervorden correlated the focal symptoms with severe cortical changes in the left temporal lobe.

The first example of this condition, however, was probably described by Fischer in 1911 in a paper on the pathology of status spongiosus. He found the typical cortical changes of this type of encephalopathy throughout both cerebral hemispheres, but more on the left side and especially in the left temporal lobe of a man of 70. The clinical details were scanty. He had had a left-sided hemiplegia ten years previously from which he had made a good recovery. Four months before his death he is described as having had another stroke

resulting in aphasia and clinical signs of severe temporal lobe disease. An old softening was found in the right thalamus but the temporal lobe disturbances were due to a diffuse cortical degeneration closely paralleling that demonstrated by Hallervorden for his case. The typical mental changes are not mentioned in the report, but so little is said on the clinical side that it would probably not be right to assume that they were absent.

The first detailed clinical and pathological account was that of Heidenhain in 1928 and it concerned 3 patients in whose brains were found cortical lesions identical with those already described, affecting in the first 2 cases the parieto-occipital regions principally, but in the third the whole cortex. In the first case status spongiosus was not present. Heidenhain emphasised the occurrence of cell shrinkage and in one case he described these cells as being present without number. He noted involvement of the striatum in Cases 2 and 3 with loss of small nerve cells, and swelling and loss of processes in those remaining. Cavitation in the corpus striatum and in the thalamus, with some loss of Purkinje cells was noted in Case 3. A prominent focal symptom in Heidenhain's cases was visual impairment progressing to cortical blindness. It was, however, eight weeks before the first and seven weeks before the second patient gave up reading. In both these patients the organic confusional state developed after this and progressed rapidly as if the pathological process was extending and building up over wider cortical fields. Incoordination and athetoid movements of the hands were noted in the later stages, possibly due to parietal lobe or striatal damage. It is not possible to feel certain of the cause of the board-like rigidity of the limbs which Heidenhain described but it is probably due to a release phenomenon following cortical and striatal damage rather than to discharging cortical lesions. In the third case the physical symptoms affecting predominantly the left arm and lasting five to six years is a highly significant feature. The cord was not examined, but it seems probable that the pathology accounting for these symptoms was similar to that which advanced so rapidly in the final four months and the severe status spongiosus in the corpus striatum and pallidal lesions may be related to this aspect of the clinical story. This is an isolated finding in about 17 cases so far recorded in whole or in part, but if it appears in other cases it must materially affect discussion as to the nature of the disease.

Our attention was first attracted to this condition in 1951 by the abnormal EEG findings in one patient, findings which, if encephalitis could be excluded, indicated a severe cerebral disorder of an unusual kind.

The striking features were the sharp wave complexes probably independent of any associated slow wave which built up synchronously in all areas of the cortex. Patterns approaching this in form have been found in all 5 cases of this disease which we have observed. In the early stages of the illness, however, sharp wave complexes may not be present, the EEG showing only generalised slow activity. In Foley and Denny-Brown's cases (1955), to be referred to later, the sharp wave complexes did not appear so that the EEG findings, while very helpful, are not necessarily diagnostic. Apart from the EEG findings our cases show that the sensory and motor cortex may be affected first, giving rise to quadriplegia instead of cortical blindness as the initial symptom. One case corresponded closely to those of Heidenhain without the intense board-like rigidity, while in another initial symptoms pointed to early involvement of the cerebellum in the disease. It is right to infer that in these instances the pathological process begins locally, either in the cortex or cerebellum and later extends in the cortex giving rise to a severe organic confusional state and later gross mental deterioration. In 2 patients, however, mental symptoms predominated and focal symptoms, while present later, were not conspicuous. Perhaps in these cases wide areas of the frontal or temporal cortex are involved simultaneously giving rise as the disease advances to severe psychic disintegration and death. All 5 cases showed myoclonic epilepsy in the later stages.

On the pathological side the cortical changes were widespread and identical with those described by Heidenhain except that the status spongiosus was more extreme in one case involving also the molecular layer. Furthermore the thalamus, corpus striatum and pallidum were severely involved in 4 of the cases. In one the cerebellum showed a status spongiosus-like lesion at the junction of the molecular and granular layer and many Purkinje cells were lost. Severe degeneration was also found in the olives in one case. In 4 out of 5 of these cases, however, there were multiple softenings in the brain lesions which could not be labelled terminal or agonal and the possible significance of these will be referred to later.

In a paper entitled "A case of senile dementia (Heidenhain's syndrome) associated with cortical blindness", Meyer *et al.* described in 1954 an instance of the disease in a man of 38 in whom mental changes appeared initially, became extreme after four months, and ended in death at six months. Here, the cortical changes were severe with gross disintegration of the occipital cortex with neuroglial reaction and myelin loss. There was also some demyelination in the occipital white matter, but whether primary or secondary to the cortical damage the authors did not discuss.

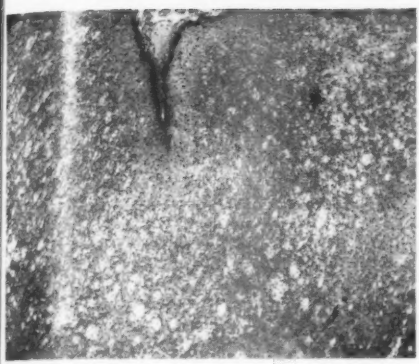


FIG. 1.—Status spongiosus of considerable degree in cortex contiguous with superior portion of right circular sulcus. Celloidin section: Mallory's phosphotungstic acid Haematoxylin ×27.

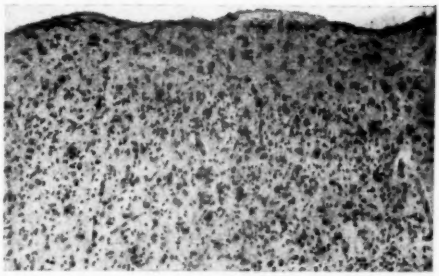


FIG. 2.—Cortex of left occipital lobe, showing considerable nerve cell loss in all layers and a marked compensatory astroglial proliferation. Frozen section: Nissl ×47.

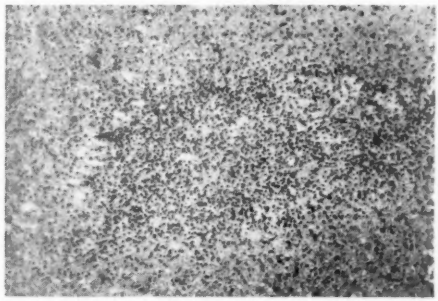


FIG. 3.—Softening in subcortical white matter of occipital lobe. Celloidin section: Haematoxylin and eosin ×47.

In 1955, Foley and Denny-Brown gave a preliminary report of two cases confirmed pathologically which add further to the clinical and pathological features of this disease. Ataxia of the trunk and limbs were initial symptoms and in the later weeks when an organic confusional state had developed, rhythmical myoclonus of the upper limbs occurred periodically associated with chewing movements of the jaw, lips and tongue. The first patient was in deep stupor, with arms adducted and semiflexed and legs extended, for seven months before death. In this case the cortical and basal ganglia atrophy was severe; the thickness of the cortex being greatly reduced and in places with hardly a viable nerve cell left. This is to be correlated with the patient having survived seven months after the disease had reached maximum, so to speak. There was also, in the patient, marked naked-eye atrophy of the cerebellum and gross degeneration of the granule layer and of the Purkinje cells with status spongiosus formation in this region. In the white matter of the brain, brain-stem, and in the pyramidal tracts there was some degeneration, considered by the authors to be secondary to the cell loss.

Two further instances of the disease studied clinically by Dr. Behrman at the Brook Hospital are at present being investigated. They showed variations of the clinical picture already described, but possibly no new features. The same may be said of two examples (Cases 1 and 3) of this disease described in 1957 by Pallis and Spillane in a paper entitled "A subacute progressive encephalopathy with mutism, hypokinesia, rigidity and myoclonus."

It cannot be disputed that we have, in the cases here referred to, a subacute progressive disease of the nervous system with consistent clinical and pathological features. The age of patients affected range from 38 to 70 years and the disease has progressed to a fatal issue in from two to six months with two striking exceptions to which reference has already been made.

The disease seems to commence sharply, if mildly, and is signalled by symptoms pointing to focal damage in any part of the cerebral hemispheres, the cerebellum or basal ganglia or by a commencing dementia, perhaps associated sometimes with such general symptoms as headache, giddiness, lassitude, insomnia, or pains in the limbs. There is some variation in the progression of the disease, symptoms advancing quickly over two to four weeks or changing little for seven to eight weeks as was the case with the visual symptoms in three patients. Also focal symptoms may advance for ten to twelve weeks before an organic confusional state develops or the latter may appear alone and advance greatly so as to make the clinical detection of late developing focal symptoms impossible.

Muscular rigidity of extreme degree and exaggerated by movement or other stimuli can occur and also a wide range of involuntary movements, tremor, athetosis or myoclonus of marked degree as well as epilepsy and myoclonic epilepsy. It seems that the myoclonus described by Foley and Denny-Brown is a unique symptom which they attribute to the combined cortical and cerebellar lesion. Also a grasp reflex is not infrequently present. The mental deterioration becomes extreme, the patient speechless, stuporous, immobile, incontinent and flaccid, or more often rigid with the arms flexed and adducted and the legs either extended or flexed. This posture has been referred to as the decorticate posture, but no postural reflexes have been described and it is doubtful if the term has any precise meaning in the human subject, as one does not know how much the rigid state is due to cortical, basal ganglia or even cerebellar damage. All investigations are more or less negative, but a slight increase of protein in the C.S.F. has been recorded. Air and arteriographic studies have not shown any striking or consistent changes.

The specific pathological changes in the cortex, basal ganglia and cerebellum, with little evidence so far of significant involvement of the brain stem or spinal cord—apart from the olives, explains the clinical picture in all its variations. The pathological changes may vary greatly in severity from case to case and from region to region.

We now come to a discussion of the nature of this disease and the first question which arises is whether it is or is not related to, or an integral part of, corticostriatospinal degeneration or Creutzfeldt-Jacob disease. Meyer *et al.* appear to consider it as a variety of the Creutzfeldt-Jacob group, for which the name Heidenhain's syndrome should be used. Bornstein and Jervis (1955) in America and Jacob *et al.* in Germany (1950) include Heidenhain's cases without question in the same Creutzfeldt-Jacob group, stating that the pathological changes are identical. Foley and Denny-Brown, in presenting their cases to the American Association of Neuropathologists, say that they have studied three patients with " Jacob's pseudosclerosis " whose clinical pictures were so distinctive and yet so different from the usual clinical and pathological description of this disease that they wished to bring it to general attention. The clinical differences between the two diseases are, therefore, admitted and it is mainly in the pathological field that doubt arises.

It might be best, therefore, first to make clear what Heidenhain thought about this problem. Although Meyer *et al.* state that Heidenhain considered his cases as closely related to Jacob's pseudosclerosis this is not how we read his paper. In fact he lists six anatomical features which distinguish them from it, viz.:

(1) The disease process exclusively affects the grey matter, is diffuse and foci are not evident.

(2) Severe affection of parts of the cortex other than the temporo-central areas, especially the occipital areas.

(3) Cell shrinkage is more marked.

(4) The glial reaction is different, *gliarasen* rosettes and neuronophagy do not occur.

(5) Fatty degeneration of neurones is not so marked.

(6) Myelin fibres are better retained.

Also he states categorically that it is not possible on account of these differences without further evidence to place his cases in the same category as Jacob's pseudosclerosis. No further evidence has appeared and we know of no reasoned answer to Heidenhain's argument. In fact the further experience of the two types of case supports Heidenhain's viewpoint. The extreme status spongiosus which can occur in the Fischer-Heidenhain type of case indicating a cytolysis of neurones rather than an atrophy and the absence of lower motor neurone involvement in the brain-stem and spinal cord are other striking differences between the two diseases.

Corticostriatospinal degeneration is a well-recognised degenerative syndrome easy to diagnose when the complete picture is present with a pathology of the same order as that

occurring in motor neurone disease but extending over wider fields in the nervous system. Even in its most acute form the pathology does not resemble that present in the encephalopathy described here. Jacob and Spielmeyer apparently knew both diseases and there is no evidence that they linked them in any way.

If then the form of encephalopathy under discussion, and which might usefully be referred to as subacute encephalopathy with spongiose atrophy of the cerebral grey matter, is different from Jacob's corticostriatospinal degeneration, of what nature is it?

Foley and Denny-Brown have postulated a primary degeneration of the neuroglia, but this viewpoint may be difficult to substantiate. Foley and Denny-Brown actually describe the neuroglial processes as cut off by the disease which could mean a destructive process involving an area of cortical groundwork carrying with it also the nervous parenchyma. If this is so then a pathology involving vascular dysfunction must first be excluded. In a paper from Maida Vale (Jones and Nevin, 1954) it was postulated that some form of vascular insufficiency at the arteriole or capillary level resulting either in stasis with fluid exudation or in impaired absorption with consequent nutritional failure could be the cause of the lesions. This was done for the following reasons, it being recognized that structural changes in the vessels were not adequate to account for any failure of the blood flow.

(1) It is certain that status spongiosus, although a non-specific change, can occur on a vascular basis, and it is difficult in the absence of any other clinical or pathological abnormality elsewhere in the body to think of any other explanation for the extreme softening of the cortex that can occur in this disease.

(2) Heidenhain in one of his cases actually described the myelinated fibres as ballooned apart by fluid, but he does not say where the fluid came from or why it appeared.

(3) The glial reaction in the disease, while not in any way specific, is such as could occur in a vascular pathology. It is not different from that which can occur in the neighbourhood of cortical softenings and is, at times, typically gemistocytic in type in the molecular layer. Also a pronounced microglial reaction or gitter cell formation can occur in the severest cases.

(4) Of the 17 cases so far known softenings have been found in no fewer than 8, good circumstantial evidence of vascular dysfunction.

It may also be mentioned that Ajuriaguerra and his co-workers (1953) in France have in fact spoken of the cortical lesion in Heidenhain's cases as possibly vascular because of the presence of status spongiosus.

One of our patients was given Priscol with such a rapid increase in the myoclonic jerks that he had to be given intravenous barbiturates, a treatment not necessary on any other occasion. One other patient had slight evidence of a shift in the arteriogram in the anterior cerebral artery possibly due to swelling of one hemisphere. Also we have some evidence, both clinically and pathologically, of this type of cortical lesion occurring in the right hemisphere of an elderly diabetic with extensive left carotid thrombosis, and EEG evidence of it occurring also temporarily in one hemisphere after removal of a meningioma. It would not be right to assume, therefore, that the condition is always fatal and it is also possible that if a vascular basis for the disease is established an effective treatment may be found.

In conclusion it seems to us also that the clinical symptoms in their great variability (pointing to disturbances in all areas of the cerebral grey matter) in their abrupt progression and occasional sudden onset, are not inconsistent with some form of vascular dysfunction.

## REFERENCES


AJURIAGUERRA, J. DE, HECAEN, H., LAYANI, F., and SADOUN, R. (1953) *Rev. neurol.*, **89,** 81.

BORNSTEIN, S., and JERVIS, G. A. (1955) *Arch. Neurol. Psychiat., Chicago*, **74,** 598.

FISCHER, O. (1911) *Z. ges. Neurol. Psychiat.*, **7,** 1.

FOLEY, J. M., and DENNY-BROWN, D. (1955) *Excerpta med., Amst.*, VIII, **8,** 782.

HALLERVORDEN, J. (1930) In: Handbuch der Geistenkrankheiten. Edited by O. Bumke. Berlin; **11,** 1094.

HEIDENHAIN, A. (1928) *Z. ges. Neurol. Psychiat.*, **118,** 49.

JACOB, H., PYRKOSCH, W., and STRUBE, H. (1950) *Arch. Psychiat. Nervenkr.*, **184,** 653.

JONES, D. P., and NEVIN, S. (1954) *J. Neurol. Psychiat.*, **17,** 148.

MEYER, A., LEIGH, D., and BAGG, C. E. (1954) *J. Neurol. Psychiat.*, **17,** 129.

PALLIS, C. A., and SPILLANE, J. D. (1957) *Quart. J. Med.*, **26,** 349.

SPIELMEYER, W. (1922) Histopathologie des Nervensystems. Berlin; **1,** 335.

[*March* 6, 1958]

## DISCUSSION ON VASCULAR DISEASE OF THE SPINAL CORD

**Dr. D. H. M. Woollam** and **Dr. J. W. Millen** (Department of Anatomy, Cambridge):

### *The Anatomical Background to Vascular Disease of the Spinal Cord*

The principles on which the vascular architecture of the spinal cord is organized can be summarized in the form of a statement by Feeney and Watterson (1946). "There exists a very close relationship between the metabolic requirements of the nervous tissue and the final distribution of intraneural vessels in the adult, a relationship which functions in such a way as to provide the nervous system with a blood supply just adequate for its minimal needs."

To put it in somewhat crude evolutionary terms, man has just as much nervous system as he can supply with oxygen and no more. Such has been the importance of the nervous system in phylogeny that it has developed to the extreme limit allowed by the vascular supply which is, in the mammal, always "just adequate for its minimal needs."

#### *The Capillary Bed of the Spinal Cord*

It is interesting therefore to note that Craigie (1955) saw anoxia as the factor responsible for the vascularization of the embryonic central nervous system. After the appearance of the earliest blood vessels in the walls of the yolk sac and gut, the neural tube is the first place to which they spread, and they reach it before it has had time to close. In the early human embryo the vessels grow along the roots of the spinal nerves centripetally. These vessels divide into dorsal and ventral branches which, by the 8 mm. stage, that is at the end of the first five weeks of pregnancy, ramify over the lateral surface of the spinal cord to form a capillary network. A few days later, at the 13 mm. stage these vessels have begun to penetrate the cord, and by the 100 mm. stage, that is at the end of the fourth month, they are evenly distributed throughout the grey and white matter.

In this way the capillary bed is formed, and since, as Scharrer (1939) has postulated, any single capillary is only able to maintain the life of nerve cells lying within half the distance to the next capillary, each and every capillary is vitally important to the integrity of the grey matter.

Now although at the 100 mm. stage, that is at the end of the fourth month of pregnancy, the white matter is equally as well vascularized as the grey, as full term approaches, the white is much less abundantly supplied with capillaries, and this condition persists throughout adult life. The poorest grey matter is indeed supplied with half as much again in capillary density as the richest white matter. There is also a tendency, albeit of a somewhat irregular nature, for the spinal cord to become more profusely vascularized as one ascends the phylogenetic scale. Mammals, for example, have a much more abundant supply altogether than any lower forms; in the rat, the white matter of the medial longitudinal bundle is as vascular as the richest grey matter of the turtle. In any animal, the vascularity of both grey and white matter differs from situation to situation. The sensory nuclei have a richer supply than the motor nuclei; the ventral horns having, for example, fewer capillaries than the most poorly supplied sensory nuclei in the cord. In the white matter also there are very considerable differences from one area to another; the pyramidal tract, for example, being twice as profusely supplied with capillaries as the fasciculus cuneatus.

The reason for these variations remains to some extent a matter for speculation. Vascular density in the grey matter has been correlated with the number of synapses (Scharrer, 1944) and with oxidase content (Campbell, 1939) and the density of mitochondria in the neurons (Scharrer, 1945); all these factors indicating that the more metabolically active the area the better is its blood supply.

#### *The Arterial Supply of the Spinal Cord*

The vessels on the anterior aspect of the cord are mainly arterial and those on the posterior surface venous, reflecting the arrangement found in the acrania and carried from these lowly forms right up the phylogenetic scale to man. There is strikingly little variation in the arrangement of the arteries and veins between the common laboratory animals and man. Since it is difficult to obtain human material fresh enough to allow of really satisfactory injection of the vascular system, we have made use of the guinea-pig and rat (Woollam and Millen, 1955*a*) to obtain a picture of the details of the vascular patterns. One general feature that is worth stressing is that *in the adult* all the vessels to be seen on the surface of the spinal cord are either arteries or veins, as there are no capillaries in the subarachnoid space.

The fusion of two longitudinal ventral anastomotic chains results in the production of the most important spinal blood vessel, the anterior (ventral) spinal artery. Cranially, this artery is formed or fed by branches from the vertebral arteries of either side and is augmented

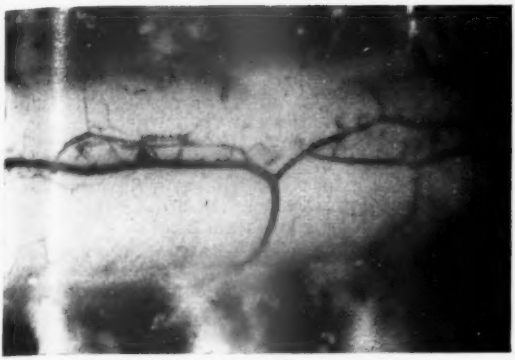


FIG. 1.—Ventral aspect of spinal cord of 24-week human fœtus. Cervical region. Injected red—blue dispersions. Mode of formation of anterior (ventral) spinal artery is shown.



FIG. 2.—Ventral aspect of spinal cord of 22-week human fœtus. Lumbar region. Injected Neoprene. Arteria radicalis anterior of Adamkiewicz (1882) is shown.

in its course by arteries derived from major vessels lying in the neighbourhood of the vertebral column. Only a relatively few of these *radicular arteries* survive into adult life, from two to seventeen, with an average of eight.

There is a major radicular artery in the cervical region which, divides into two branches which really *are* the anterior spinal artery (Fig. 1). This particular specimen illustrates how tempting although quite unjustified it is to speculate as to the direction of flow in the arterial system on the results of the injection of cadavers. In Table I the radicular contributions are

TABLE I.—RADICULAR CONTRIBUTIONS IN CERVICAL REGION

| | Anterior spinal artery | | Posterior spinal arteries |
|---|---|---|---|
| Level of spinal cord | Major radicular contributions | Minor radicular contributions | Minor radicular contributions |
| Cervical | One at C6–C7 (C8 not higher than C6) | 3–5 at levels above C6 | One at C2 |
| Thoracic | 0 | 0–2 at C8–T9 | One–3 at C5–C7<br>0 in upper thoracic |
| Lumbar | One (Adamkiewicz) at T10, L1, L2 (T9–L3) | One occasionally at T9–10 (not below L3) | Every 2nd dorsal root from T4–L4 |
| Total | 8 (Range 2–17) | | 16 (Range 10–23) |

divided into major and minor vessels. It will be seen that the two most important arterial contributions are the large cervical vessel and the arteria radicalis anterior of Adamkiewicz (1882) in the upper lumbar region. This latter vessel is, in fact, the largest supplying the anterior spinal artery, being invariably greater in size than the contribution from the vertebral artery. It is generally unilateral (Fig. 2) and is twice as common on the left as on the right side (Kadyi, 1889).

The anterior spinal artery may be duplicated in parts, generally in the cervical region, possibly because it is formed not by a process of *obliteration* of one or other of two ventral anastomotic chains as they come together at various levels, but by a process of *fusion* of these chains throughout their length (Torr, 1957). In the thoracic region the anterior spinal artery is quite tenuous, has few radicular contributions, and may even be absent for a few centimetres. It is extremely difficult to inject in human specimens and everything points to the view that the flow in the anterior spinal artery is directed from above and below towards the thoracic region.

The anterior spinal artery supplies the whole of the grey matter with the exception of part of the dorsal horn which receives its blood from the posterior spinal chains. The main branches of the anterior spinal artery are the *central* branches. Since these represent the survival of parts of the originally paired ventral anastomotic chains, they do not generally bifurcate except possibly in the lowest part of the cord, but they pass alternately to either side, entering the grey matter of the ventral horn. When the anterior spinal artery is double, the central branches invariably go to the ipsilateral side (Tureen, 1938). There are about two hundred central branches in all, that is one to every 2 mm. of spinal cord. In the human there are about eighty in the thoracic region, forty-five in the cervical, thirty-five in the lumbar region and twenty-five in the sacral region. Their *density* is, however, at its *lowest* in the thoracic region and at its greatest in the cervical and lumbar enlargements of the cord. On the average each central artery supplies 15 to 20 mm. of spinal cord and some supply as much as 40 to 50 mm. Since there is one central branch for every 2 mm. of cord, there is considerable overlap in the capillary bed, and this makes good the inadequate supply at the termination of individual branches. There is, however, no anastomosis between adjacent central branches. The arrangement of the central branches ensures that every group of cells receives blood from several branches and every branch supplies several groups of cells. The white matter receives terminal branches from the grey matter which it encloses.

In addition to central branches the anterior spinal artery has slender lateral and ventral branches which are not so regularly segmental as the central branches. The ventral branches spread over the surface of, and partially supply, the ventral columns of white matter. The lateral branches pass round to join the posterior lateral chains, thus completing a system which is akin to the circle of Willis.

The posterior or dorsal arterial system consists of two quite widely separated chains running just medial to the emerging dorsal nerve roots. They are formed in a similar fashion to the anterior spinal artery without the final fusion of the two elements. The radicular contributions which they receive pass along the dorsal roots, and are few in number in postnatal life (Table I). These dorsolateral chains have branches similar to the central branches of the anterior spinal artery, which are best developed in the cervical region of the cord. These penetrate the cord to form, with the ramifications of the central branches of the *anterior* spinal artery, the richest of all the anastomoses in the cord in the sensory nuclear masses at the base of the dorsal horn.

*The Venous Drainage of the Spinal Cord*

The veins form a much more complex network than the arteries but six main channels can be distinguished, an anterior and a posterior channel, and in addition two antero-lateral and two postero-lateral channels. The most significant channel is the anterior one, the anterior spinal vein, which lies deeper than the artery, and never crosses its anterior surface. The anterior spinal vein or veins is formed from central veins which accompany the central artery. The central vein does not, however, cover the same territory as the central artery, there are no longitudinal tributaries running with the longitudinal branches of the arteries and each central vein is capable of draining less blood than its artery can supply.

Veins accompany the ventral and dorsal nerve roots and drain the six longitudinal channels. These veins do not correspond with the arteries. They are in number 35–60 with an average of 38 so that half the nerve roots possess radicular veins (Table II). The anterior radicular

TABLE II.—SITUATION OF RADICULAR VEINS

| Level of spinal cord | Anterior radicular veins | Posterior radicular veins |
|---|---|---|
| Cervical | Evenly distributed small in diameter | Many small |
| Thoracic | Evenly distributed small in diameter | Moderate number of small |
| Lumbar | Larger L5 particularly | Few small |
| Sacral | Largest S1–S2 particularly | None |

veins are best developed in the lumbar and sacral regions of the spinal cord and the *fifth lumbar root* in particular generally carries a large radicular vein. Conversely the posterior radicular veins are less numerous and virtually absent in the lower cord.

In the cervical and thoracic regions, several radicular veins may unite to form a single vein at the dura. The spinal radicular veins lying inside the subarachnoid space pierce the dura to communicate with the internal vertebral venous plexuses. The venous sinuses thus formed, lying immediately outside the dura clothing the spinal nerve, are extremely well developed and tortuous, they are important because they have opening into them the spinal arachnoid villi through which cerebrospinal fluid is probably absorbed into the venous system.

*The Perivascular Spaces*

There remains a further important point about the spinal vascular supply which is worthy of consideration, and this is the perivascular relationship of the central vessels (Woollam and Millen, 1954, 1955*b*). The arteries and veins on the surface of the cord lie in the subarachnoid space. As each central artery enters the substance of the cord it carries with it pial and arachnoidal layers which fuse together in the substance of the ventral horn to form a *true* perivascular space, a cul-de-sac communicating with the subarachnoid space. Similar pockets of subarachnoid space accompany the large veins but do not penetrate so deeply. The capillaries do not possess either a perivascular sheath or a perivascular space and are separated from the neurons only by ground substance and the perivascular processes of astrocytes (Woollam and Millen, 1955*c*).

*Conclusions and Summary*

The situation of the perivascular spaces and arachnoid villi, the distribution of the central arteries and the varying dimensions of the capillary bed and, in particular, the peculiar arrangement of the radicular arteries and veins afford the basis for an almost kaleidoscopic range of patterns upon which pathological processes may be organized or disseminated.

*Acknowledgments.*—We wish to express our gratitude to Professor J. D. Boyd for his advice in the preparation of this paper. Our thanks are also due to Mr. J. F. Crane for the photographs.

REFERENCES

ADAMKIEWICZ, A. (1882) *S.B. Akad. Wiss. Wien*, Abt. III, **85,** 101.
CAMPBELL, A. C. P. (1939) *Arch. Neurol. Psychiat., Chicago*, **41,** 223.
CRAIGIE, E. (1955) In: Biochemistry of the Developing Nervous System. Edited by H. Waelsch. New York; p. 28.
FEENEY, J. F., and WATTERSON, R. L. (1946) *J. Morph.*, **78,** 231.
KADYI, H. (1889) Uber die Blutgefässe des Menschlichen Rückenmarkes. Leipzig.
SCHARRER, E. (1939) *Anat. Rec.*, **75,** 319.
—— (1944) *Quart. Rev. Biol.*, **19,** 308.
—— (1945) *J. comp. Neurol.*, **83,** 237.
TORR, J. B. D. (1957) *J. Anat., Lond.*, **91,** 587.
TUREEN, L. L. (1938) *Res. Publ. Ass. nerv. ment. Dis.*, **18,** 394.
WOOLLAM, D. H. M., and MILLEN, J. W. (1954) *Biol. Rev.*, **29,** 251.
——, —— (1955*a*) *J. Neurol. Psychiat.*, **18,** 97.
——, —— (1955*b*) *J. Anat., Lond.*, **89,** 193.
——, —— (1955*c*) Proceedings of Second International Congress of Neuropathology. Amsterdam; p. 367.

**Dr. W. Blackwood** (National Hospital for Nervous Diseases, London):

For convenience I propose to divide the possible conditions of vascular disease of the spinal cord into two groups: (1) in which the vascular lesions in the spinal cord are predominantly due to vascular obstruction, and (2) in which they are predominantly due to hæmorrhage. With my colleagues, I have searched the records of the National Hospital from 1909 to 1958, and in 3,737 post-mortems—the majority of which were done by Dr. Greenfield—we have found only 9 cases of obstructive lesions and 2 cases of hæmorrhage. 11 cases in 3,737 are very few. They may actually be rare, or such patients may not have been admitted to the hospital, or they may not have died in the hospital, or the central nervous system may not have been fully examined. I think this last is unlikely in cases presenting with symptoms or signs of spinal cord involvement, but I must admit to its possibility in patients who did not show such symptoms or signs, for the spinal cord is not examined in all cases.

TABLE I.—CASES OF OBSTRUCTION

The National Hospital, Queen Square
1909–1958. 3,737 Autopsies

| | | | |
|---|---|---|---|
| Atherosclerosis | 0 | Polyarteritis nodosa | 0 |
| Hypertensive vascular disease | 0 | Arteritis following spinal anæsthesia | 0 |
| Arterial thrombosis | 0 | Dislocation of the odontoid | 1 |
| Bland embolism | 0 | Herniated cervical intervertebral discs | 3 |
| Infected embolism | 0 | Dissecting aneurysm of the aorta | 1 |
| Nitrogen embolism | 0 | Subacute necrotic myelitis | 4 |

Table I lists all the conditions which I thought could, directly or indirectly, cause obstructive lesions of the spinal blood vessels. The obstructive possibilities of atherosclerosis, of hypertensive vascular disease, or arterial thrombosis, of embolism and of polyarteritis nodosa

do not require explanation. Arteritis is a very rare complication of spinal anæsthesia. The cases which Greenfield *et al.* reported in 1955 did not die at the hospital. Dislocation of the odontoid and herniated cervical intervertebral discs may both be associated with ischæmic necrosis of the spinal cord, so may a dissecting aneurysm of the aorta. Subacute necrotic myelitis is associated with thrombosis of spinal veins. The figures refer to the number of cases of each condition which we found. Of those conditions listed in the first column, of which we did not find any examples, some are of particular interest. It is perhaps surprising that we found no examples of lesions due to those two very common conditions of *atherosclerosis* and *hypertensive vascular disease*, but this negative finding is in accordance with Staemmler's observations in 1939. He examined 600 spinal cords from patients of all ages, two-thirds of them being in the 5th to 8th decades. He found that in cases of generalized atherosclerosis the arteries of the spinal cord were not at all or only insignificantly involved and that in hypertensive cases there was only a minor degree of change.

*Nitrogen embolism* has become of increasing importance. Originally it occurred when divers were decompressed too quickly but it is now more commonly encountered following rapid exposure to actual or simulated high altitude. Patients who survive for a period often show regions of hæmorrhage or of ischæmic necrosis in the spinal cord, particularly in the thoracic segments. Haymaker (1957) considers that involvement of the spinal cord is due to embolism by bubbles of nitrogen which appear in the blood stream after the reduction of atmospheric pressure, together with embarrassment of the spinal vertebral venous circulation by gas bubbles arising in the epidural and/or retroperitoneal fat.

I turn now to the conditions of which we have examples. The vascular lesions in the cord accompanying *dislocation of the odontoid process* and *herniated cervical intervertebral discs* are of similar pathogenesis. In dislocation of the odontoid the anterior spinal artery is compressed against the body of the 2nd cervical vertebra. Mair and Druckman reported the present cases of herniated cervical intervertebral discs in 1953. They found that the lesions in the white matter are regions of ischæmic necrosis, that there is also necrosis in the anterior horns of grey matter, and that the composite distribution of the lesions from several cases coincide with the field of distribution of the anterior spinal artery and its branches, which are, presumably, compressed by the herniated discs.

We have had one case of infarction of the spinal cord in association with a *dissecting aneurysm of the aorta*, which was published by Thompson in 1956. In this condition, there is massive and extensive hæmorrhage into the media of the aorta. The hæmorrhage surrounds, stretches and may even tear the intercostal and lumbar arteries or obliterate their lumen. The portion of the cord which is constantly and most severely damaged is the mid- and lower thoracic region, which is normally supplied by intercostal arteries which are almost invariably damaged by the aneurysm. The cranial part of the cord which derives its blood supply from the vertebral arteries and the supra-aortic intercostals is seldom involved. The lumbosacral portion of the cord which is supplied by the lumbar, ileolumbar and lumbosacral arteries is only occasionally damaged. The ischæmic necrosis always involves the grey matter and adjacent white matter. For some unknown reason the peripheral white matter is often spared.

There have been 4 cases of *subacute necrotic myelitis*. At post-mortem, there may or may not be an obvious varicose condition of the surface veins over the thoracic and lumbosacral segments. It was present in 2 of our cases. On section of such cases one finds patchy necrosis of the cord from the mid-thoracic region downwards. The small blood vessels within the spinal cord show mural, often hyaline, thickening. The surface veins are thickened as well as varicose, and contain thrombus which may be recent (Mair and Folkerts, 1953) but is usually organized and may be recanalized. Some people consider that this condition is primarily an angiomatous malformation with secondary thrombosis. Others consider that it is primarily thrombophlebitis with secondary varicosity. I would suggest that we have not yet got sufficient evidence to be certain of the pathogenesis. In particular we need more information about the state of the paravertebral and lumbar veins.

We turn now to the vascular lesions in the spinal cord which are predominantly due to hæmorrhage.

TABLE II.—CASES OF HÆMORRHAGE

The National Hospital, Queen Square
1909–1958. 3,737 Autopsies

| | | | |
|---|---|---|---|
| Aneurysm, True .. .. | 0 | Aneurysm, False with coarctation of the aorta .. | 1 |
| Hypertensive hæmorrhage | 0 | Hæmatomyelia from angiomatous malformation .. | 1 |

Table II lists the conditions which might give rise to hæmorrhage into the spinal cord and the figures show the number of cases which we found. There were no records of any true

aneurysms, either congenital saccular or mycotic, or of hypertensive hæmorrhage. There was one false aneurysm and one example of hæmatomyelia.

The *false aneurysm* arose in relation to a dilated anterior spinal artery in a case of *coarctation of the aorta* of adult type. In this condition the aorta is narrowed or occluded distal to the left subclavian artery at or just below the aortic insertion of the ductus arteriosus, which is almost always obliterated. The aortic obstruction prevents the arterial blood from reaching the lower part of the body by the usual route. An anastomotic circulation develops, which includes the anterior spinal artery. The blood from the heart can enter the anterior spinal artery from the upper radicular arteries, can pass down the anterior spinal artery and can re-enter the aorta through lower radicular arteries (Edwards *et al.*, 1948). The portion of the anterior spinal artery which takes part in the anastomosis becomes dilated. A similar involvement of the cervico-thoracic portion of the anterior spinal artery had occurred in our case of a girl who died at the age of 18 and was found to have a ruptured false aneurysm at the level of the 1st thoracic segment (Fig. 1).

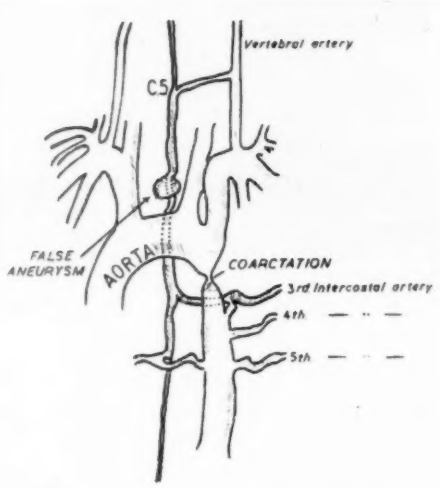



FIG. 1.—Diagram illustrating false aneurysm of anterior spinal artery in coarctation of the aorta, based upon the post-mortem notes (Dr. J. G. Greenfield) of the case mentioned and Fig. 1 of the article by Edwards *et al.* (1948).

We have had one case of true hæmatomyelia or massive bleeding into the spinal cord. This was a case with bleeding from a localized angiomatous malformation at L.1, published by Richardson in 1938. From the angioma, blood tracked cranially and caudally in the posterior columns.

At this point I should like to say a word or two against the concept of so-called traumatic hæmatomyelia. It is true that after a severe traumatic injury of the spine, the naked-eye appearance of the cord will often be those of a very hæmorrhagic lesion of the cord at the level of the injury, together with a thin column of blood-stained material which runs caudally and cranially from this site, possibly for several segments. Gordon Holmes in 1915, describing acute spinal injuries of warfare, showed conclusively that this blood-stained material was produced at the site of the maximal damage by suddenly applied mechanical forces, that it had been squeezed cranially and caudally along lines of least resistance, and that it consisted principally of disintegrating nervous tissue together with a small amount of blood. His findings have since been repeatedly confirmed. Fig. 2 is an example of fracture dislocation of the cervical region in a woman who was injured in a car crash two weeks before she died. The myelin preparations show the state of the cord at three levels. Microscopical examination at many levels showed that the material in the posterior columns which had presumably come from the level of the fracture was composed of necrotic disintegrating cord tissue (Fig. 3). The material was not blood and the condition is therefore not one of ***hæmatomyelia.***

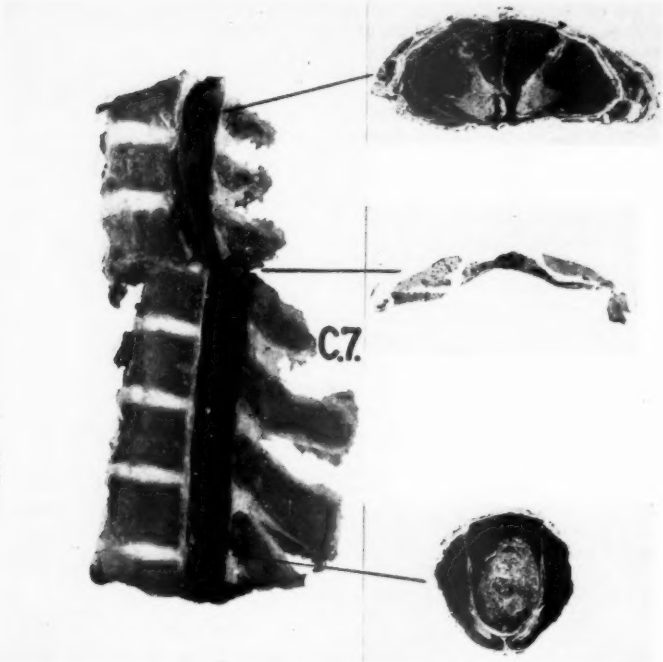



FIG. 2.—Sagittal section of cervical vertebræ and myelin preparations of spinal cord, at the levels indicated, of a woman who died two weeks after breaking her neck in a motor-car accident. The vertebræ and spinal cord were removed, and fixed *en bloc*, by courtesy of Sir William Bentley Purchase and Dr. F. E. Camps. In the region of the dislocation the cord is reduced to a ribbon within an unbroken pia-arachnoid.

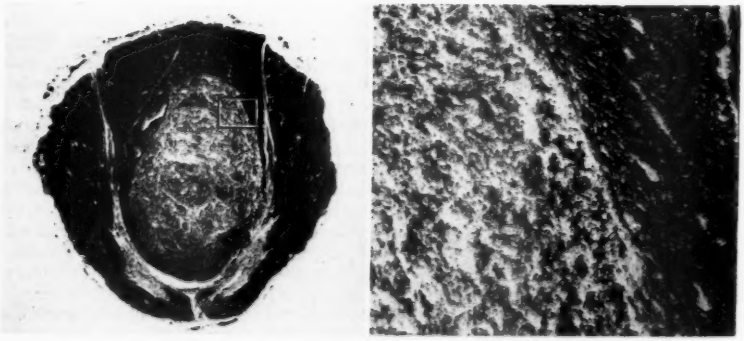


FIG. 3.—*Left*—Myelin preparation of spinal cord from caudal level in Fig. 2. Within the posterior white columns is a mass of abnormal material. *Right*—Higher power view of white square in previous picture, which confirms that most of the abnormal material has the histological character of disorganized white matter. Celloidin. Loyez ×60.

*Summary*

When we compare our findings on vascular disease of the spinal cord with what we know about vascular disease of the brain, certain features emerge: (1) vascular disease of the spinal cord is much less frequent than vascular disease of the brain. In particular atherosclerosis and hypertensive vascular disease do not appear to affect the spinal cord appreciably. (2) Congenital saccular aneurysms hardly ever occur.

We do not have the necessary factual data to explain this: We need to know more about the circulation of the spinal cord in health and in disease, both during life and at post-mortem. At post-mortem we need to examine not only the intradural vessels but also the arteries and veins which connect the spinal cord with the general circulation. When we think of how much has been added to our knowledge of vascular disease of the brain by the exploration of the whole length of the carotid and vertebral arteries, we may hope that more detailed examination of similar vessels in the cord will add much to a rather neglected subject.

*Acknowledgments.*—I am indebted to Drs. M. Crompton, H. Hetzel, D. D. Layton and O. M. Reinmuth for assistance with searching the records, and to Mr. J. A. Mills for the photographs.

## REFERENCES

EDWARDS, J. E., CLAGETT, O. T., DRAKE, R. L., and CHRISTENSEN, N. A. (1948) *Proc. Mayo Clin.*, **23**, 333.

GREENFIELD, J. G., RICKARDS, A. G., and MANNING, G. P. (1955) *J. Path. Bact.*, **69**, 95.

HAYMAKER, W. (1957) *Handb. Spez. Path. Anat. Hist.*, Berlin, **13**, part 1B, 1600.

HOLMES, G. (1915) *Brit. med. J.*, ii, 769.

MAIR, W. G. P., and DRUCKMAN, R. (1953) *Brain*, **76**, 70.

——, and FOLKERTS, J. F. (1953) *Brain*, **76**, 563.

RICHARDSON, J. C. (1938) *Brain*, **61**, 17.

STAEMMLER, M. (1939) *Z. Neurol.*, **164**, 179.

THOMPSON, G. (1956) *Brain*, **79**, 111.

**Mr. Joe Pennybacker** (Radcliffe Infirmary, Oxford):

It will be apparent from the previous papers that vascular lesions of the cord are not often surgical affections. And yet I suppose that for every spinal tumour that the surgeon sees he will be asked to see three or four patients with vascular lesions of one of the types described by Dr. Blackwood. Clinically these fall into three groups: those in which the disturbance of cord function comes on suddenly or in a matter of a few minutes, those in which it takes twenty-four to seventy-two hours to become complete, and those in which it is a much more chronic process occurring over a period of weeks, months or years. The very acute ones may occur like a bolt from the blue, without any evidence to indicate the cause of the lesion, or there may be a vague history of some apparently trivial injury or infection. It is usually painless, and the spinal cord lesion is complete. X-rays and lumbar puncture are normal, and if a myelogram is done it is usually normal too. This is the clinical picture of what has long been called transverse myelitis, and although inflammation may be the responsible factor in some cases, I suspect that in the majority it is a vascular lesion. Not often do these patients die in the acute stage, and if they are explored surgically, it is usually impossible to differentiate between inflammation and infarction or hæmorrhage in the substance of the cord. In the circumstances I have described it is most unlikely that operation has anything to offer, but as with some traumatic lesions of the spinal cord, it may be difficult to withhold an exploration if for no other reason than to exclude absolutely a compressing lesion.

At the other extreme are the very chronic processes, the best example of which are the angiomas or angiomatous malformations of the cord. The history of the myelopathy in this condition is very similar to that of compression of the cord by a benign tumour, and as they are coarse and obvious lesions, we see them not infrequently at operations, indeed on 16 occasions among 390 explorations for focal lesions of the cord in our clinic. A patient may bear one of these lesions through a long life without much trouble coming from it. The specimen illustrated in Fig. 1 came from a man of 82 who recently died of prostatic disease in the Cowley Road Hospital, Oxford. The only neurological defect that he is known to have had was a drop-foot on the left side, and the muscles of the anterior tibial compartment were atrophied in a way suggesting that this may have been due to a local muscular lesion rather than to disturbed innervation. And yet there was this extraordinary tangle of blood vessels on the surface of the cord and in the cauda equina and many abnormal vessels in the cord itself (Fig. 2). There were no visible areas of infarction in the cord, however, and this is consistent with the absence of neurological signs.

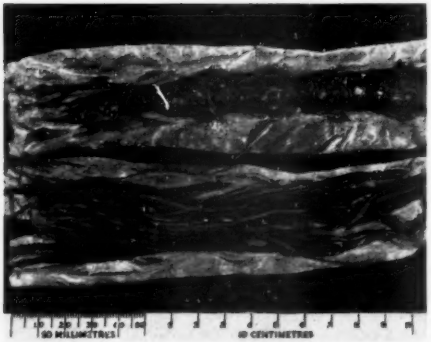


FIG. 1.—Angiomatous malformation of spinal cord and cauda equina.

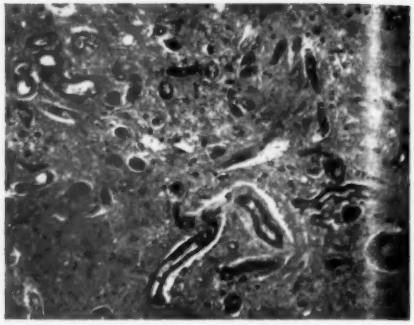


FIG. 2.—Photomicrograph (× 90) of cord showing abnormal vessels.

More commonly, the story is that of back pain, not necessarily very severe, which may go on for two or three years before the onset of the neurological deficit, and this is usually a slowly progressive paraplegia with proportional sensory loss and sphincter paralysis. X-rays of the vertebral column are normal, and lumbar puncture usually reveals no complete manometric block, but almost invariably an increase in the protein content of the fluid. Myelography reveals no obstruction but there may be an irregular curved or scalloped pattern where the contrast medium is caught up in loops of abnormal vessels, and this is characteristic of these lesions. The clinical picture is that of a paraplegia rather than a tetraplegia because angiomas are much commoner in the dorsal and lumbar cord than in the cervical region. We have had only one case in which the cervical enlargement was affected, and in this there was a history of pain in the neck for ten years before the onset of a symmetrical lower motor neurone paralysis of both upper limbs with preservation of power in the lower limbs, and an incomplete and dissociated sensory loss extending from C.2 to Th.4 level. The picture was thus similar to that seen in syringomyelia; it differed in that although there was no complete manometric block on lumbar puncture, the fluid was yellow and contained 2·5 grams % of protein. At the exploration the cervical enlargement was found to be invested in a serpiginous mass of tangled blood vessels, largely but not completely filling the theca. These lesions cannot be removed because what is visible on the surface is only a part of the abnormality: there are abnormal vessels in the substance of the cord as well, and it is occlusion of them with resulting infarction which produces the disability. This patient carried on for another five years before his legs became paralysed, however.

A great deal has been written about these lesions. In the German literature it is spoken of as angiodysgenetische myelomalacia (Bodechtel and Erbslöh, 1957) and the French call it the Foix-Alajouanine disease. It is well described in Wyburn-Mason's monograph (1943) and there has recently been an interesting account by Newman (1958) of angiomas in the vertebræ and extrathecal space, as well as of the cord, producing symptoms which are aggravated during pregnancy, something that we have seen occasionally too. I should also add that we have had three patients with cord compression by a hæmangioblastoma, and in addition to the discrete tumours, there was a more diffuse vascular abnormality of the cord, but not quite as extensive or striking as the ones we have been discussing. These patients had all had cerebellar hæmangioblastomas removed, but there is no reason why the spinal lesion should not occasionally declare itself before the cerebellar one.

Should these lesions be explored? If the myelopathy is progressive and there is impending disability, I think they should be explored, because occasionally the pre-operative diagnosis will be wrong and a benign lesion will be found which can be removed. If the diagnosis proves to be correct, the lesion should be left alone. In these circumstances it is sometimes asked whether radiation treatment is worth while. I think the answer is "no" because the nutrition of the cord already depends on the precarious blood supply transmitted by pathological vessels and any encroachment by thrombosis could only have an adverse effect.

I should now turn to a more common problem, and that is the middle group of subacute lesions. In these there is interference with the blood supply of the cord, often by lesions in the extrathecal space, such as abscesses, granulomas and neoplasms. Three or four times a year we are asked to see patients with a rapidly progressive paraplegia, developing in circumstances which might indicate an extrathecal abscess. There is usually a history of a generalized or focal infection; there is pain in the back at an appropriate level, perhaps slight local

tenderness but no other superficial signs of inflammation. The sensory and motor loss develop *pari passu* and rapidly, and the cord lesion may become complete in twenty-four to forty-eight hours of the onset. There is no manometric block on lumbar puncture, and the fluid may contain only a slight excess of protein. X-rays of the vertebral column are normal. If these patients can be seen before the lesion is complete—and this is much more nearly possible to-day than was the case fifteen or twenty years ago—the affected area of the cord should be explored quickly, before the lesion is complete. This is indeed one of the few emergencies in spinal cord surgery, and an operation in the middle of the night will occasionally reveal an extradural abscess, granuloma, cyst or neoplasm. The simple relief of tension in the vertebral canal afforded by the laminectomy may be of benefit, and if an abscess is drained or a tumour removed, even though only partially, the blood supply of the cord improves and there may be a dramatic recovery of function; if, on the other hand, the lesion is complete when the patient is first seen and has been so for days or weeks, operation has little to offer. But even these patients deserve careful myelography, because occasionally something quite unusual is encountered.

In May 1956 a man (F. B., R.I. No. 224978) of 48 years was admitted with an almost complete transverse lesion of the cord at the 2nd thoracic segment. A week before admission he had been in another hospital because of a large abscess on the right knee. On the day after admission he noticed that his legs were weak and numb, he became incontinent of fæces and was unable to pass urine. It appears that the paraplegia became complete in the day or so following. X-rays of the vertebral column were normal and a lumbar puncture revealed no block and only 40 mg. of protein in the fluid. He was transferred to us under suspicion of having an extrathecal abscess related to the infection of the knee-joint. On admission, both lower limbs were flaccid, and the only voluntary movement was feeble flexion of the right toes. The reflexes in the lower limbs and abdomen were abolished. There was a sharp sensory level at the 2nd thoracic level affecting all modalities incompletely down to the level of the umbilicus below which there appeared to be total sensory loss. Myelography showed that the contrast medium ran freely up to the skull, but there appeared to be slight enlargement of the cord opposite the 7th cervical vertebra.

There was thus considerable evidence against a remediable lesion, i.e. a profound cord lesion with no manometric block, normal spinal fluid, and so little in the way of myelographic obstruction. But I had seen this man as an outpatient eight months before. He had epilepsy due to cysticercosis and at this time he walked with a slight limp. He had in fact a mild Brown-Séquard syndrome at this time; a slight spastic weakness of the left lower limb and slight spinothalamic sensory impairment down the right side. He was much less concerned about this than the epilepsy, however, and it was with some difficulty that we discovered how the spinal cord lesion had developed. Two and a half years before he had a severe pain between the shoulder blades which went on for about eight weeks and then cleared up. He was then aware of some numbness in the lower abdomen and a slight weakness of the left leg. He did not think these had altered at all until the acute episode accompanying the abscess of the knee.

The possibility of a cysticercosis in the cord was thus a real one and that was what was found at operation. The lower part of the cervical cord was a little swollen and a small incision about a centimetre long disclosed the bluish wall of a cyst. This protruded under its own pressure until it was a mass about the size of the tip of one's thumb. The cyst then ruptured and a little watery fluid escaped. It was then simply lifted out with forceps. It proved to be a multilocular cyst containing a cysticercus with suckers and hooklets (Fig. 3).

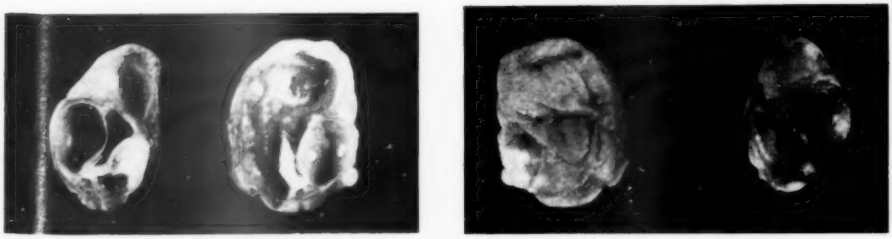


FIG. 3.—Multilocular intramedullary cysticercus cyst (1·8 cm. × 1·2 cm. × 1 cm.).

This man made a very good recovery. On the day after operation there was a striking return of power and sensation and within a month he was walking fairly well and had reasonable control of his sphincters. I saw him again recently, eighteen months after operation, when the power in the lower limbs was normal, but a disturbance of postural sensibility made the gait a little awkward, somewhat like a tabetic. It was still possible to demonstrate a qualitative difference in sensation below the 2nd thoracic level. He had good control of his sphincters but there was still some urgency of micturition.

This case demonstrates the necessity for exploration in some instances, even though the contrary evidence may be impressive. There is another group in which this is also true, and that is in some cases of paraplegia due to carcinoma of the prostate. In most of these there are deposits in the vertebræ with collapse and compression of the cord and for these operation has very little to offer. There are some, however, in which the vertebræ are intact and a progressive paraplegia develops. The lesion is usually in the mid-thoracic region and as is common with extrathecal lesions, the motor loss is usually more profound than the sensory deficit. There is little or no pain, lumbar puncture reveals no block and the fluid is normal. Myelography is likewise normal, or it may show a little constriction of the column, enough to indicate that there is a mass in the extrathecal space. These lesions are worth exploring because there is usually a pad of neoplasm infiltrating the extrathecal connective tissue and adherent to the theca, but not apparently exerting much pressure. Removal of what can be seen, followed by irradiation and hormone treatment, may bring about very considerable improvement and allow these patients to lead fairly active lives for another three or four years.

Paraplegia may also result from extravertebral lesions which interfere with entering blood vessels. We have seen this in carcinoma of the lung with glandular involvement along the vertebral column, and with neuroblastomas arising from the sympathetic chain in the thorax. The mechanism in these cases is similar to that in the acute paraplegias which have occasionally followed thoraco-lumbar sympathectomy and the use of a long-lasting local anæsthetic injected into the intercostal neurovascular bundle for the relief of post-operative pain. For these laminectomy is not called for, although in the case of benign extravertebral lesions, operation may be beneficial in arresting a progressive paraplegia.

In summary, surgical experience indicates that in the vast majority of spinal cord affections in which there is no manometric block and no myelographic obstruction, operation does not help, but there are a few cases in which an exploration is justified even on flimsy evidence. Many of these will be unrewarding, but in some an operation may mean literally the difference between life and death.

I am indebted to Dr. L. Cosin for the specimen illustrated in Fig. 1 and to Dr. David Oppenheimer for his help.

## REFERENCES

BODECHTEL, G., and ERBSLÖH, F. (1957) *Handb. Spez. Path. Anat. Histol., Berlin*, **13**, 1576.

WYBURN-MASON, R. (1943) The Vascular Abnormalities and Tumours of the Spinal Cord and its Membranes. London.

NEWMAN, M. J. D. (1958) *J. Neurol. Psychiat.*, **21**, 38.

# Section of Endocrinology

President—C. N. ARMSTRONG, M.D., F.R.C.P.

[*February* 26, 1958]

## Some Observations on the Mechanism of Insulin Action in Muscle

By P. J. RANDLE, M.A., Ph.D., M.B., B.Chir., and G. HOWARD SMITH, M.A., B.Sc., Ph.D.

*Cambridge*

ACCORDING to the permeability hypothesis of insulin action in muscle, insulin increases glucose uptake by accelerating its entry into the muscle cell (Levine and Goldstein, 1955; Park *et al.*, 1955; Park and Johnson, 1955). While there is much experimental evidence to support this hypothesis nothing has been known of the processes which restrict the entry of glucose into muscle cells under normal conditions or of the mechanism of this effect of insulin. We have shown elsewhere that the uptake of glucose by isolated rat diaphragm muscle, incubated in a medium buffered with bicarbonate, is increased by anoxia and by 2 : 4-dinitrophenol, sodium arsenite, sodium cyanide or sodium salicylate, as well as by insulin (Randle, 1956; Randle and Smith, 1957; Manchester *et al.*, 1958). Each of these factors, except insulin, is known to inhibit the production of energy-rich phosphate compounds by respiration (oxidative phosphorylation). These observations therefore led us to suggest that energy-rich phosphate compounds are required for the process which restricts the entry of glucose into muscle cells of isolated diaphragm under basal conditions (Randle and Smith, 1957).

In an attempt to obtain more direct evidence for this suggestion we have studied the effect of each of these factors on the accumulation of two sugars, D-glucose and D-xylose in isolated rat diaphragm. The accumulation of xylose was studied in addition to the accumulation of glucose because, unlike glucose, xylose is not appreciably metabolized by isolated diaphragm (Kipnis and Cori, 1957). Since glucose is metabolized by diaphragm its accumulation is affected both by the rate of entry into the muscle and by the rate of utilization within the muscle. On the other hand the accumulation of xylose in diaphragm depends only on the rate at which it enters the muscle.

The experiments were carried out with a diaphragm preparation described by Kipnis and Cori (1957) in which no muscle fibres are cut. Diaphragm was incubated for one hour in a bicarbonate-buffered medium containing glucose or glucose + xylose. After incubation the concentration of glucose or xylose in both muscle and medium was determined and the glucose or xylose space calculated. The glucose or xylose space is that fraction of the volume of a tissue containing fluid of the same specific gravity and sugar content as the incubation medium. To interpret these results in terms of the distribution of the sugar between extracellular and intracellular water, the glucose or xylose space is compared with the volume of extracellular fluid. Free sugar is deemed to be present in intracellular water only if the glucose or xylose space exceeds the volume of extracellular fluid. The volume of extracellular fluid was determined in these experiments by measuring the space occupied by inulin or thiosulphate, substances which are generally held to be confined to extracellular water under normal conditions.

Under basal conditions free glucose in diaphragm was found to be confined to extracellular water (*cf.* Park *et al.*, 1955). When insulin, cyanide or salicylate was present or oxygen excluded glucose uptake increased, but free glucose remained confined to extracellular water. These observations suggest either that the rate of utilization of glucose within the cell proceeds at a much faster rate than the entry of glucose into the cell such that no free glucose accumulates, or alternatively that glucose does not enter the cell as the free sugar. When arsenite or 2 : 4-dinitrophenol was present glucose uptake increased but some free glucose accumulated in intracellular water. When fluoride was included in addition to 2 : 4-dinitrophenol, in order to inhibit utilization of glucose, still more glucose accumulated in intracellular water. Thus unless glucose enters by an abnormal process in the presence of arsenite, dinitrophenol or fluoride it would appear that glucose does enter intracellular water as the free sugar but that it may only be detected in intracellular water when its utilization within the muscle cell has become rate-limiting.

A small amount of xylose entered intracellular water when diaphragm was incubated under basal conditions. The penetration of diaphragm by xylose was found to be rapid and almost all the xylose which accumulated during one hour of incubation entered the muscle during the first ten minutes. This suggests that there is some barrier within the muscle cell which confines xylose to a small fraction (10–15%) of the intracellular water under basal conditions. In the presence of insulin, 2 : 4-dinitrophenol, sodium arsenite, cyanide or salicylate or in the absence of oxygen further accumulation of xylose occurs and the sugar comes into equilibrium with 40–80% of intracellular water.

These observations are compatible with the views that the uptake of glucose by muscle is limited by the rate of entry of glucose into the muscle cell and that insulin, anoxia or substances which inhibit oxidative phosphorylation increase glucose uptake by speeding its entry into the cell. They also appear to show that the sugar xylose is confined to a small fraction of the volume of extracellular water under basal conditions by a process dependent upon energy-rich phosphate. Although no direct evidence has been obtained on this point it would nevertheless seem reasonable to conclude that glucose is similarly confined to a small fraction of the volume of intracellular water under basal conditions. Insulin does not inhibit oxidative phosphorylation (Stadie, 1954) and the mechanism of its effect on glucose uptake is therefore likely to differ from that of factors which do inhibit oxidative phosphorylation. One possibility is that insulin may act by restricting the access of energy-rich phosphate to a process concerned with the regulation of glucose entry.

It has been shown in the present investigation that salicylate, like insulin, increases the uptake of glucose by isolated diaphragm and promotes the entry of xylose into the cells of diaphragm. Salicylate is known to reduce glycosuria and lower blood sugar in diabetic patients (Reid *et al.*, 1957) and in several forms of experimental diabetes (Ingle, 1950; Smith, 1952; Smith *et al.*, 1952). The present observations suggest that salicylate may exert its antidiabetic effect by increasing the utilization of glucose by muscle.

We wish to thank Professor F. G. Young, F.R.S., for much valuable discussion and encouragement. The cost of these investigations was largely defrayed by a grant for research expenses from the Medical Research Council to one of us. (P. J. R.). A full account of these investigations will be published in the *Biochemical Journal.*

REFERENCES

Ingle, D. J. (1950) *Proc. Soc. exp. Biol., N.Y.*, **75**, 673.
Kipnis, D. M., and Cori, C. F. (1957) *J. biol. Chem.*, **224**, 681.
Levine, R., and Goldstein, M. S. (1955) *Recent Progr. Hormone Res.*, **11**, 343.
Manchester, K. L., Randle, P. J., and Smith, G. H. (1958) *Brit. med. J.*, i, 1028.
Park, C. R., Bornstein, J., and Post, R. L. (1955) *Amer. J. Physiol.*, **182**, 12.
——, and Johnson, L. H. (1955) *Amer. J. Physiol.*, **182**, 17.
Randle, P. J. (1956) *Nature, Lond.*, **178**, 983.
——, and Smith, G. H. (1957) *Biochim. biophys. Acta*, **25**, 442.
Reid, J., Macdougall, A. I., and Andrews, M. M. (1957) *Brit. med. J.*, ii, 1071.
Smith, M. J. H. (1952) *Biochem. J.*, **52**, 649.
——, Meade, B. W., and Bornstein, J. (1952) *Biochem. J.*, **51**, 18.
Stadie, W. C. (1954) *Physiol. Rev.*, **34**, 52.

## Corticotrophin Tests in Hirsute Women

By J. D. N. Nabarro, M.D., F.R.C.P., Audrey Moxham, J. D. H. Slater, M.B., M.R.C.P., and G. Walker, M.B., M.R.C.P.

*London*

Corticotrophin gel stimulation tests have been performed on 33 women with "idiopathic hirsutism" in an attempt to obtain more information about the ætiology of this condition. The patients were selected for severity of the hirsutism, associated menstrual abnormality or complaint of sterility. All had male distribution of pubic hair. None of them showed the clinical features of Cushing's syndrome. In 12 the urinary 17-ketosteroid excretion exceeded 15 mg./day.

*Methods.*—Single injections of 100 units of corticotrophin gel were given daily for three consecutive days. Adrenal cortical response was assessed by estimating the urinary total 17-hydroxycorticosteroids (17-OHCS) by the method of Appleby *et al.* (1955), with slight modifications (Moxham and Nabarro, 1956); 17-ketosteroids (17-KS); and urinary pregnanediol (PD) and pregnanetriol (PT) by the method of Bongiovanni and Clayton (1955). High figures for urinary pregnanediol were confirmed by the method of Klopper *et al.* (1955). In many cases a simple paper chromatographic fractionation of the 17-KS has been performed for the detection of an increased output of dehydroepiandrosterone (DHIA).

*Results.*—In a series of women without hirsutism or adrenal dysfunction, steroid excretions on the third day of stimulation were found to be 17-OHCS<120 mg./24 hr.; 17-KS<45 mg. (21 patients); PD<10 mg. and PT<5 mg./24 hr. (13 patients). The results in the hirsute women are shown in Fig. 1. The maximum excretion of 17-OHCS exceeded the normal range in 15 patients, of 17-KS in 24, of PD in 9 and of PT in 6 patients.

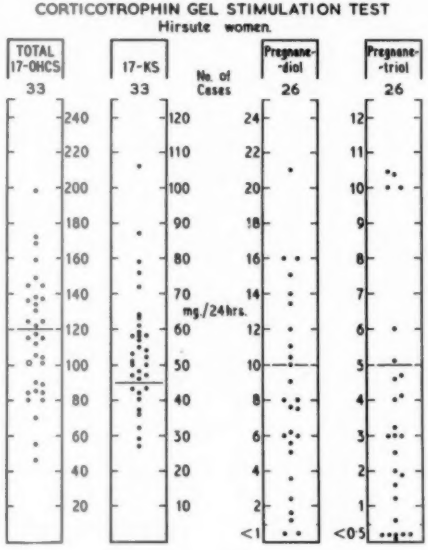



FIG. 1.—Urinary steroid excretion on third day of corticotrophin gel test. The lines indicate the highest levels obtained in normal subjects.

The patients have been divided into four clinical groups: gross hirsutism starting during adolescence—19 patients, of whom 12 were obese (Group I) and 7 thin (Group II); gross hirsutism starting after pregnancy—8 patients all of whom were obese (Group III); and 6 obese patients with moderate hirsutism (Group IV). The results of the corticotrophin stimulation tests in the various groups may be summarized as follows (the numbers in brackets are the total number in each category):

| Groups | | I | II | III | IV |
|---|---|---|---|---|---|
| Abnormal increase of 17-KS | Resting 17-KS<15 mg./d. | 3(6) | 1(4) | 4(5) | 5(6) |
| | Resting 17-KS>15 mg./d. | 6(6) | 2(3) | 3(3) | 0 |
| Abnormal increase of 17-OHCS | | 7(12) | 0(7) | 4(8) | 4(6) |

*Comment.*—Abnormal urinary 17-KS excretion, either resting or following stimulation was anticipated in a proportion of these hirsute patients but the increased response of 17-OHCS, PD and PT was rather surprising.

17-OHCS excretion on the third day of corticotrophin was abnormal in 15 patients ranging from 122–198 mg./24 hr. It has not been possible to make any detailed study of the steroids measured but in a few cases 17-ketogenic steroids (17-KGS) and 17-hydroxycorticoids (17-OHs) have been measured by modifications of the methods of Norymberski *et al.*(1953) and Reddy *et al.* (1952). The results were as follows:

| | | | | | | |
|---|---|---|---|---|---|---|
| 17-OHCS | 122 | 137 | 144 | 144 | 164 | 198 |
| 17-KGS | 106 | 107 | — | 86 | — | — |
| 17-OHs | 88 | 81 | 58 | 82 | 74 | 104 |

The increased excretion of 17-OHCS following corticotrophin might be associated with obesity rather than hirsutism. Poisnick and Di Raimondo (1956) have reported that obese women have an increased response to corticotrophin but they found that the resting 17-OHCS excretion was at the upper limit of normal and the ratio Stimulated : Resting steroid output was not increased. In our study 32 normal subjects gave a ratio $6{\cdot}3 \pm 1{\cdot}64$, whereas in 26 hirsute obese women it was $10{\cdot}1 \pm 3{\cdot}86$. In the 7 non-obese hirsute patients the mean ratio was 6·8, and in 4 obese non-hirsute ones 6·5.

Increased excretion of PD and PT only occurred in association with an abnormal response of 17-OHCS and does not suggest the presence of a metabolic block. The increase probably represents an overflow into the circulation and urine of metabolites of intermediaries in the synthesis of 17-OHCS.

One purpose of this study was to determine whether an adrenal abnormality could be demonstrated in any hirsute women whose resting 17-KS excretion (quantitatively and qualitatively) was within normal limits. The results are summarized in the following table:

| Group | No. | Resting 17-KS raised | Resting 17-KS normal: DHIA increased | Resting 17-KS normal: No increase DHIA. Increased response to corticotrophin | Resting 17-KS normal: No evidence of Adrenal dysfunction |
|---|---|---|---|---|---|
| Gross hirsutism | | | | | |
| Adolescence— obese I | 12 | 6 | 0 | 4 | 2 |
| — not obese II | 7 | 3 | 1 | 0 | 3 |
| Post-partum— obese III | 8 | 3 | 3 | 1 | 1 |
| Moderate hirsutism— obese IV | 6 | 0 | 0 | 6 | 0 |
| Total | 33 | 12 | 4 | 11 | 6 |

An adrenal abnormality was demonstrated in 27 of the 33 patients, in 11 it was only detected by the corticotrophin test. This does not mean that the hirsutism is of adrenal origin and the disappointing results of adrenalectomy and adrenal suppression might make such an assumption appear unjustified. It is possible that in these cases the hirsutism is initiated by an abnormality of adrenal function but that after a time the hair follicles become independent of continued hormonal stimulation. Adrenal suppression would therefore have to be started as early as possible if it is to influence this distressing and common condition.

*Summary.*—Adrenal cortical stimulation tests have been performed on 33 hirsute women. An abnormal increase of the urinary 17-ketosteroids was found in 24 patients, of 17-hydroxycorticosteroids in 15, of urinary pregnanediol in 9 and of pregnanetriol in 6.

An adrenal abnormality was detected in 27 of the 33 women, in 11 the only evidence of this was an increased response in the corticotrophin test.

We wish to thank our colleagues for allowing us to study their cases and the Clinical Research Committee of the Middlesex Hospital for the provision of laboratory facilities and a personal grant to J. D. N. N.

REFERENCES

APPLEBY, J. I., GIBSON, G., NORYMBERSKI, J. K., and STUBBS, R. D. (1955) *Biochem. J.*, 60, 453
BONGIOVANNI, A. M., and CLAYTON, G. W. (1954) *Bull. Johns Hopk. Hosp.*, **94**, 180.
KLOPPER, A., MICHIE, E. A., and BROWN, J. B. (1955) *J. Endocrin.*, **12**, 209.
MOXHAM, A., and NABARRO, J. D. N. (1956) *J. clin. Path.*, **9**, 351.
NORYMBERSKI, J. K., STUBBS, R. D., and WEST, H. F. (1953) *Lancet*, i, 1276.
POISNICK, J., and DI RAIMONDO, V. (1956) *J. clin. Endocr.*, **16**, 957.
REDDY, W. J., JENKINS, D., and THORN, G. W. (1952) *Metabolism*, **1**, 511.

## The Importance of Differential Assay of Urinary FSH and ICSH

By P. S. BROWN, B.M., M.R.C.P.

*Birmingham*

RECENTLY there has been considerable progress in establishing the assay of urinary gonadotrophins as a precise and practicable procedure. A reference substance has been provided by the Medical Research Council and various convenient techniques have been described for the assay (for review *see* Loraine, 1956). In most cases they measure what may be termed "total gonadotrophin", i.e. the combined and probably synergistic effect of follicle stimulating hormone (FSH) and interstitial cell stimulating hormone (ICSH). These methods are better than the older semi-quantitative ones because they are precise and give the result in terms of a standard.

In considering various clinical situations it is usual to think in terms of FSH and ICSH as distinct entities with distinct actions, and the concept of total gonadotrophin is of limited usefulness. The possibility of differentiating between the two gonadotrophins in urinary extracts was therefore investigated.

The methods used for the extraction and measurement of urinary gonadotrophins have

been described in detail elsewhere (Brown, 1955, 1956). Two methods of assay are used and in both the extract is injected into immature female mice. In one assay the uterus is weighed and this is taken to measure total gonadotrophin as defined above. In the other assay an excess of human chorionic gonadotrophin (HCG) is injected at the same time as the extract and the ovaries are weighed. The excessive luteinizing effect of the HCG minimizes the effect of any ICSH in the extract and augments the response to FSH. The assay therefore measures mainly FSH and the specificity of such a method has been shown by Steelman and Pohley (1953). In both assays a substandard to the M.R.C. reference substance is used.

The assay of FSH, being relatively specific, gives a direct measure of this hormone and the assay of total gonadotrophin is used for comparison with this. From such a comparison the content of ICSH in the extract can be inferred. If the ratio of FSH to ICSH is the same in the unknown and the standard then the results of both assays will be the same. If the unknown is relatively deficient in FSH the potency estimated by the assay of total gonadotrophin will be higher than that estimated as FSH. If the unknown has relatively less ICSH the potency by the assay of FSH will be the higher. This may give the impression of the part being greater than the whole, but it must be realized that the two assays measure different things and the activity of the standard in one assay is not necessarily equivalent to its activity in the other.

Table I is compiled from results of assays on material from non-pregnant patients with

TABLE I.—GONADOTROPHINS FROM AMENORRHŒIC PATIENTS ASSAYED BY TWO METHODS

| Source of extracts | Total pairs of assays | Cases in which results conflicted | | |
|---|---|---|---|---|
| | | Total | ICSH low | FSH low |
| Amenorrhœic patients (standard from post-menopausal women) | 45 | 9 | 7 | 2 |
| Amenorrhœic patients before and during hormone treatment | 16 | 5 | — | — |

primary or secondary amenorrhœa: some of the results have been reported in detail elsewhere (Brown, 1956; Fletcher and Brown, 1957). Parallelism could be tested and was satisfactory in all the assays except a few in which the highest dose of unknown caused no response. In these cases the organ weight was shown to be significantly ($P<\cdot05$) less than that of mice treated with the lowest dose of standard so that an upper limit could be set on the potency. The two assays were taken to show significantly different results when the 95% fiducial limits did not overlap.

Nine out of the 45 pairs of assays on extracts from these patients gave contrasting results by these criteria and in others there were differences which did not reach this high degree of significance. In 16 other instances the urinary gonadotrophins were compared by both methods before and during treatment with cortisone or œstrogen. In nearly a third of these instances the assays gave significantly different results, showing differences in response of the two gonadotrophins to the treatment. Thus in these clinical situations nearly a quarter of the pairs of assays gave more information than either assay would have done alone.

When the urinary gonadotrophins were studied during the normal menstrual cycle the two assays gave very different pictures, there being more than threefold differences in results at some stages of the cycle.

It is concluded that in the study of either pathological or physiological material the use of two methods of assay gives qualitative as well as quantitative information. If only total gonadotrophin is assayed the qualitative information will be lost and the result in some cases may be actually misleading. The two assays used in the present investigation are clinically practicable. The animals used and their manipulation are the same as in the older semi-quantitative assays. The number of animals required for the assay of total gonadotrophin may be only two or three times as many as are used in these older methods. The precision of the assay of FSH has recently been improved to the extent where a similar number of animals is needed. This has become possible by stricter selection of animals and the use of HCG prepared and standardized in the laboratory.

I am very grateful to Dr. A. C. Crooke in relation to all aspects of this work, and to the Endowment Fund Medical Research Committee of the United Birmingham Hospitals for a grant.

REFERENCES

BROWN, P. S. (1955) *J. Endocrin.*, **13**, 59.
—— (1956) *J. Endocrin.*, **14**, 129.
FLETCHER, R. F., and BROWN, P. S. (1957) *Clin. Sci.*, **16**, 669.
LORRAINE, J. A. (1956) *Vitam. and Horm.*, **14**, 306.
STEELMAN, S. L., and POHLEY, F. M. (1953) *Endocrinology*, **53**, 604.

[*March* 26, 1958]

# The Urinary Excretion of Œstrogens, Pregnanediol and Pituitary Gonadotrophins During the Menstrual Cycle [*Abridged*]

By J. B. BROWN, M.Sc., Ph.D., A. I. KLOPPER, B.Sc., Ph.D., M.B., M.R.C.O.G.,[1] and J. A. LORAINE, M.B., Ph.D., M.R.C.P.(Ed.)

*Clinical Endocrinology Research Unit (Medical Research Council), University of Edinburgh*

THE urinary excretion of œstrogens, pregnanediol and pituitary gonadotrophins was studied throughout nine ovulatory menstrual cycles. Particular attention was given to correlating the cyclical changes in the excretion of one hormone with those of the others. Basal temperature records were also kept and where possible any change in basal temperature was correlated with the pattern of hormone excretion.

Seven of the 9 subjects were healthy women engaged in their normal activities; 1 of these was artifically inseminated and became pregnant during the period of observation. The remaining 2 were patients in hospital suffering from mammary carcinoma; 1 of these was treated by ovarian irradiation during the period of study. There was no history of previous menstrual abnormalities in any of the subjects investigated.

Urinary œstrone, œstradiol-17β and œstriol were determined by the method of Brown (1955*a*). Urinary pregnanediol was estimated by the method of Klopper *et al.* (1955). Gonadotrophins were extracted from urine by the method of Loraine and Brown (1956*a*, *b*) and were assayed biologically by (i) the uterine weight test in intact immature mice, and (ii) the ventral prostatic weight test in hypophysectomized rats. Estimations by the mouse uterus test were performed in all 9 subjects; in 3 subjects parallel assays by the two tests were performed. Assay results by both methods were calculated in terms of HMG-20A and were expressed as "HMG units per twenty-four hours".

Only assay methods of proved reliability were used in this study. It is therefore likely that the results reported herein are more meaningful from the quantitative point of view than any previously reported. The reliability criteria of the individual methods have been reviewed elsewhere (Coyle *et al.*, 1956; Brown *et al.*, 1957; Loraine, 1958).

The most notable feature of the results obtained was the constancy of the hormonal excretion pattern from one individual to another although the actual quantities excreted varied considerably in different subjects. The values obtained for the excretion of œstrogens and pregnanediol were quantitatively very similar to those reported by Brown (1955*b*) and by Klopper (1957) in a previous series of cases.

In all 9 subjects in whom the urinary gonadotrophin excretion was estimated by the mouse uterus test the output during the follicular and luteal phases of the cycle was low, being generally less than 10 HMG units per twenty-four hours. In 7 of the 9 cases a definite peak in gonadotrophin excretion ranging from 13 to 40 HMG units per twenty-four hours was observed at approximately mid-cycle; in the remaining two subjects this rise was absent. In one patient with mammary carcinoma the gonadotrophin excretion was studied first during a menstrual cycle and secondly subsequent to ovarian irradiation. It was found that immediately after radiotherapy the excretion values rose steeply and approximately one month after treatment were some twenty times higher than those found in the follicular and luteal phases of the cycle.

When gonadotrophin assays were conducted by the mouse uterus and hypophysectomized rat prostate tests it was noted that the results obtained agreed very closely and that the ratio of potencies of the two methods one to another was approximately unity at all stages of the cycle. A similar observation has recently been made by Buchholz (1957). It is generally believed that the amounts of FSH and ICSH elaborated by the anterior pituitary fluctuate independently during the menstrual cycle. Since the two assay methods presumably measure different types of gonadotrophic activity, it might have been anticipated that the presence in urine of variable proportions of FSH and ICSH would be reflected in varying potency ratios. The finding throughout of a potency ratio in the neighbourhood of unity suggests either that the extract contains a single gonadotrophin with two activities or that it contains two gonadotrophins which are always present in the same relative proportions. The fact that ICSH activity as determined by the hypophysectomized rat prostate test, could usually be demonstrated in urine at all stages of the menstrual cycle conflicts with the generally accepted view that this hormone is secreted only at the time of ovulation and in the early luteal phase of the cycle.

[1]Present address: Obstetric Medicine Research Unit, Aberdeen University Medical School Foresterhill, Aberdeen.

Peaks of excretion of œstrogens and of gonadotrophins were characteristic features at mid-cycle. The present study has demonstrated that the relationship in time of these two peaks is variable. In some individuals the two peaks occurred simultaneously; in others the gonadotrophin peak followed the œstrogen peak by periods ranging from one to four days. It is of considerable interest that in none of the subjects studied did the gonadotrophin peak precede the œstrogen peak. If the assumption is made that gonadotrophins are eliminated in urine as rapidly as œstrogens, it would appear reasonable to conclude that the peak of œstrogen excretion could not have been initiated by the increase in gonadotrophin output.

In 7 out of 8 subjects the luteal phase rise in pregnanediol occurred at approximately the same time as the rise in basal temperature; in one patient there was no increase in basal temperature during the luteal phase but the pattern of hormone excretion was normal. The luteal increase in urinary pregnanediol occurred after the œstrogen peak, the time interval ranging from one to four days.

In the majority of subjects the overall rise and fall of œstrogen levels paralleled those of pregnanediol. However there appeared to be no correlation between the actual amounts of œstrogen and pregnanediol excreted.

One patient in the present series was successfully inseminated and became pregnant during the period of study. The pregnancy proceeded uneventfully to term. The first indication that pregnancy had supervened was a sharp rise in gonadotrophin excretion occurring nine days after insemination; it is possible that this rise was due to the presence in urine of human chorionic gonadotrophin (HCG) rather than pituitary gonadotrophins. The increase in gonadotrophin excretion was followed by a rise in œstrogen excretion and a maintenance of the high luteal phase level of pregnanediol. In this patient the insemination was performed on the day of the cycle in which the peak of excretion of œstrone and œstradiol-17β was expected. It is of interest to note that previous inseminations performed at the time of the rise in basal temperature had been unsuccessful.

The substance of this paper will be published in full in the *Journal of Endocrinology*.

REFERENCES


Brown, J. B. (1955*a*) *Biochem. J.*, **60**, 185.
—— (1955*b*) *Lancet*, i, 320.
——, Bulbrook, R. D., and Greenwood, F. C. (1957) *J. Endocrin.*, **16**, 41.
Buchholz, R. (1957) *Z. ges. exp. Med.*, **128**, 219.
Coyle, M. G., Mitchell, F. L., and Russell, C. S. (1956) *J. Obstet. Gynæc., Brit. Emp.*, **63**, 560.
Klopper, A. (1957) *J. Obstet. Gynæc., Brit. Emp.*, **64**, 504.
——, Michie, E. A., and Brown, J. B. (1955) *J. Endocrin.*, **12**, 209.
Loraine, J. A. (1958) The Clinical Application of Hormone Assay. Edinburgh; Chapters I and II.
——, and Brown, J. B. (1956*a*) *J. clin. Endocrin.*, **16**, 1180.
——, —— (1956*b*) *J. Endocrin.*, **14**, xxxi.


## Some Effects of 17α-Ethyl-19-Nortestosterone in Man


By F. T. G. Prunty, M.D., F.R.C.P., R. V. Brooks, Ph.D., Barbara E. Clayton, M.D., Ph.D., and R. R. McSwiney, M.B.

*Department of Chemical Pathology, St. Thomas's Hospital Medical School*


This substance has been examined for its effect in balance studies, adrenal steroid suppression, gonadotrophin suppression and androgenicity. Doses of 100 mg. per day intramuscularly, or orally have been used and are now regarded as excessive, 50 mg. per day appears as effective and may also be too large. In all of 10 patients nitrogen retention occurred, the average in 6 over two weeks of treatment being 3·0 grams per day. There have been interesting effects on calcium balance, significant falls in fæcal calcium occurring, particularly during the first week. There has been a uniform fall of urine calcium, which appears to persist during treatment (average 49 mg. per day, range 14–154 mg.). In all instances phosphorus retention was proportional to nitrogen and calcium. Potassium retention has exceeded the requirement of nitrogen by about 8 mEq. per day. Sodium and water retention can occur, but not consistently. In view of the tendency for nitrogen and particularly fæcal calcium to "escape" a long term study was made in a boy with fragilitas ossium. Control nitrogen retention (1·4 grams per day) increased to 2·9 grams on 50 mg. ethyl nortestosterone and calcium balance became positive (135 mg. per day). After six months treatment nitrogen retention was only 1·0 gram but calcium 178 mg. Urine calcium also remained at half the control level of 115 mg. per day. During these six months weight gain was 6·5 kg. with clinical development of muscle, compared with no weight gain during the six months preceding treatment.

The only significant alteration in serum chemistry has been in the phosphorus level, which falls about 20% and appears to continue with treatment. In a breast cancer patient serum phosphorus rose from 3·4 to 6·6 mg.% after oophorectomy and during forty-two days of therapy remained below 3·0 mg.%.

The steroid should suppress the catabolic effects of cortisone and prednisone, and has been of value in this respect in 2 patients with skin disease who developed osteoporosis due to large doses of these substances. The pattern of response was similar to that in the first group of patients and the fall in fæcal calcium appeared not to persist.

A fall in both urine ketosteroids and ketogenic steroids was noted. In 5 patients ketosteroids fell significantly (4 male and an oophorectomized female for breast cancer). The ketogenic steroids fell in the males but, curiously, not in the woman. The ketosteroids were studied in detail by the method of Brooks (1958), in 3 of the males and the woman. There was a significant fall in the steroids of adrenal origin: dehydroepiandrosterone (1 male excepted) and 11-hydroxyætiocholanolone, the latter primarily arising from cortisol (Dorfman, 1954). The corresponding 11-keto compound, present in small amounts also fell. The adrenal ketosteroid $\triangle^4$-androstenedione is normally metabolized to androsterone and ætiocholanolone (which also arise from testosterone). The intramuscular administration of approximately 45 mg. of androstenedione to a male with peptic ulceration resulted in a recovery of approximately 45% of the dose as these two metabolites and the amount was not altered by simultaneous administration of ethylnortestosterone. This shows that the reduction of the adrenal component of these two metabolites by ethylnortestosterone is not due to altered metabolism. That there is such a reduction of the adrenal component was well shown in the oophorectomized woman. There may, of course, be in the male also a suppression of testosterone secretion, but we have no direct evidence for this.

The effect of ethylnortestosterone on gonadotrophin excretion in 4 patients with elevated resting levels (Turner's syndrome, post-menopause and eunuchoidism) has been studied. Doses of 100 to 150 mg. per day produced little evidence of suppression, except possibly in one patient during the second week of treatment.

There is no doubt that ethylnortestosterone has androgenic properties. This point has been studied in the breast cancer patient, 2 eunuchoids and a boy of 5 years with fragilitas ossium. It seems markedly less androgenic than testosterone, but continued use of 20 mg. daily for seven weeks produced penile enlargement and visible growth of pubic hair in the small boy. Further experience is required to appraise its real clinical usefulness as an anabolic agent.

REFERENCES

BROOKS, R. V. (1958) *Biochem. J.*, **68**, 50.
——, and PRUNTY, F. T. G. (1957) *J. Endocrin.*, **15**, 385.
CLAYTON, B. E., and PRUNTY, F. T. G. (1958) *J. Endocrin.* In Press.
DORFMAN, R. I. (1954) *Recent Progr. Hormone Res.*, **8**, 5.
MCSWINEY, R. R., and PRUNTY, F. T. G. (1957) *J. Endocrin.*, **16**, 28.

## Some Observations on Adrenocorticotrophin in Blood

By BARBARA E. CLAYTON, M.D., Ph.D.

*Department of Chemical Pathology, St. Thomas's Hospital Medical School, London*

ADRENOCORTICOTROPHIN (ACTH) assays have been performed by the method of Sayers *et al.* (1948), using unextracted plasma or serum from patients and animals respectively. Analysis of assay data obtained using commercial preparations of ACTH and our own colony of rats, showed that provided at least 4 rats were injected with a single dose of plasma or serum, and that the mean depletion of ascorbic acid produced by the single dose of unknown was at least 60 mg. then 0·6 i.mu. ACTH could be detected 95 times out of 100. Hypophysectomized rats tolerate 2 ml. and frequently 4 ml. of plasma or serum injected intravenously per 100 grams body-weight. The assay therefore detects 15 i.mu. ACTH/100 ml. plasma or serum. ACTH is therefore not detected in the blood of normal patients or unstressed animals.

Most assays have been semiquantitative only and performed according to the method of Brill *et al.* (1956). That the results are of the right order of magnitude is supported by the following experiment. A preparation of pituitary ACTH (J 10602, Armour Laboratories Limited) was assayed against La–1–A and a patient with rheumatoid arthritis was then infused intravenously with it at the rate of 184 i.mu./minute. Prior to infusion her plasma contained no detectable ACTH. Towards the end of the infusion, her plasma was assayed and found to contain 36·1 i.mu. ACTH/100 ml. The theoretical concentration of ACTH

would be 30·7 i.mu./100 ml. plasma, presuming that the half-life of ACTH is five minutes, and that it is confined to the vascular compartment (Sayers, 1955).

The concentration of ACTH in the plasma of some patients is given in Table I. It is generally agreed that ACTH is readily detectable in untreated Addison's disease (Sydnor *et al.*, 1953) and a raised level was found in Mrs. W. (Table I). Miss B. and Mr. H. were

TABLE I.—ACTH IN THE PLASMA OF SOME PATIENTS

| Diagnosis | Patient | Plasma ACTH i.mu./100 ml. |
|---|---|---|
| Untreated Addison's disease | Mrs. W. | 16 in 1951<br>23 in 1954 |
| Suspected Addison's disease, not confirmed on further investigation .. .. .. | Miss B. | Less than 15 |
| | Mr. H. | 46 |
| Cushing's syndrome .. .. .. .. | Mrs. C.* | 145 |
| | Miss D.† | Less than 15 |
| | Mr. B.‡ | 50 |
| | Mr. L.§ | 38 |
| Scurvy .. .. .. .. .. .. | Miss M. | Less than 15 |
| | Mr. U. | Less than 15 |

*Adrenal hyperplasia; no pituitary lesion apparent; resting 17-ketosteroids (KS) and 17-ketogenic steroids (KGS) were high; no response to ACTH test.

†A pituitary lesion may be present; resting KS and KGS were high, but there was a further response to administered ACTH.

‡Adrenal hyperplasia and a pituitary chromophobe adenoma enlarging and involving the optic chiasma were present.

§At the time of the ACTH assay, this patient was adrenalectomized and maintained on cortisone. A pituitary lesion of unknown pathology was present.

patients admitted to hospital with a provisional diagnosis of Addison's disease, which in fact was not confirmed on further investigation. Both complained of lassitude, and had marked pigmentation of their bodies and mouths. Miss B. showed an excellent response to a standard ACTH test (Prunty, 1956) with increased urinary steroids and marked sodium retention. No ACTH was detectable in her plasma. Though Mr. B. responded to a standard ACTH test, sodium retention was poor and his urinary excretion of 17-ketogenic steroids did not exceed 37 mg./day. His plasma ACTH was however high, and it is perhaps possible that he was in the process of developing classical Addison's disease, especially as his history only extended back two months.

Details concerning 4 patients with Cushing's syndrome are given in a footnote to Table I. Plasma ACTH was high in 3 of them. In 9 patients reported in the literature with Cushing's syndrome (Taylor *et al.*, 1949; Sydnor *et al.*, 1953; Paris *et al.*, 1954) significant depletion in the Sayer's test was only found in 2; of these, 1 had an adrenal tumour and 1 had adrenal hyperplasia. No pituitary lesion was described in any of their patients.

The occurrence of ACTH in blood following adrenalectomy has been studied in animals. ACTH is not detectable in unstressed normal male rats. Following adrenalectomy and maintenance on glucose-saline solution, ACTH was not detectable in pooled serum collected from rats one week, or four, or eight months after operation, but after three weeks 17 i.mu. ACTH/100 ml. serum was found. Barrett *et al.* (1958) have also reported an increase in ACTH after twenty-one, but not after six days. Failure to detect ACTH after four and eight months could be due to hypertrophy of extra-adrenal tissue with the consequent production of corticoids or to compensatory secretion of corticoid-like substances by the testes, or to an ultimate adaptation by the animal so that increased production of secretion of ACTH by the pituitary ceases. No macroscopic extra-adrenal tissue was demonstrated in any of the rats after four or eight months, nor were there any changes in the amount and structure of the interstitial tissue of the testes of rats adrenalectomized for four months.

Following the cessation of oral maintenance therapy with cortisone in adrenalectomized guinea-pigs, the animals will survive for a period of up to four weeks. While on cortisone therapy ACTH is not detectable in adrenalectomized guinea-pigs, nor is it detectable two, three, ten, eleven or nineteen days after withdrawal of cortisone. It has been detected twenty-one, twenty-three and twenty-seven days after the withdrawal of cortisone, the levels found being, 37, 34 and 15 i.mu. ACTH/100 ml. serum respectively. Withdrawal of cortisone in adrenalectomized guinea-pigs is presumably equivalent to adrenalectomy in the rat, and in both species ACTH in the blood does not reach detectable levels for three weeks. In patients too, in whom one would expect ACTH to be high, withdrawal of cortisone for two weeks, is frequently not sufficient for it to return to detectable levels.

REFERENCES

BARRETT, A. M., HODGES, J. R., and SAYERS, G. (1958) *J. Endocrin.*, **16**, xiii.
BRILL, A. B., ELY, R. S., DONE, A. K., AINGER, L. E., and KELLEY, V. C. (1956) *J. clin. Endocrin.*, **16**, 262.
PARIS, J., UPSON, M., Jr., SPRAGUE, R. G., SALASSA, R. M., and ALBERT, A. (1954) *J. clin. Endocrin.*, **14**, 597.
PRUNTY, F. T. G. (1956) *Brit. med. J.*, ii, 615, 673.
SAYERS, G. (1955) *J. clin. Endocrin.*, **15**, 754.
SAYERS, M. A., SAYERS, G., and WOODBURY, L. A. (1948) *Endocrinology*, **42**, 379.
SYDNOR, K. L., SAYERS, G., BROWN, H., and TYLER, F. H. (1953) *J. clin. Endocrin.*, **13**, 89.
TAYLOR, A. B., ALBERT, A., and SPRAGUE, R. G. (1949) *Endocrinology*, **45**, 335.

# The Neural Intermediate Lobe Hormone ("B")

By F. W. LANDGREBE, D.Sc., and G. M. MITCHELL, M.B.

*Welsh National School of Medicine, Cardiff*

EXTRACTS of the pituitary gland exhibit many pharmacological activities. Of the various activities found in extracts of the gland, the melanophore expanding was one of the first to be recognized as a hormone in amphibia over thirty years ago by Hogben. It caused a darkening of the skin so that the animal appeared black on a white background and he called it "B-hormone" (Hogben and Slome, 1931). After a dorsal lymph-sac injection of the extracts into frogs and toads, he measured the expansion of the melanophores of the skin according to an arbitrary scale (Hogben and Gordon, 1930).




FIG. 1.—The assessment of the melanophore index (M.I.) after Hogben and Slome (1931).

Landgrebe, Stehle, Waring and others spent many years developing methods of manufacture of "B" from the posterior lobes of domestic animals such as the pig and ox and we have finally obtained from pig posterior lobe pituitary an extract with a potency of about 1,000 i.u./mg. (Landgrebe and Mitchell, 1954). This was subjected to electrophoresis and the product, a pure polypeptide, contained about 1,500 i.u./mg. Harris and Roos (1956) determined the amino-acid sequence of this material.

TABLE I.—AMINO-ACID SEQUENCE OF "B" FROM PIG GLANDS (HARRIS AND ROOS, 1956)

| Asp. | Glu. | Gly. | Pro. | Tyr. | Lys. | Met. | Glu. | His. | Phe. | Arg. | Try. | Gly. | Ser. | Pro. | Pro. | Lys. | Asp. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |

"B"-containing extracts can be obtained from the pituitary glands of many other than domestic animals. It is present in large amounts in extracts of the hypophysis of man, ox, guinea-pig, horse, sheep, reptiles (turtles and alligators) and toads. Houssay has found it in the skate pituitary in which the neural lobe is very rudimentary. Table II shows the

TABLE II.—AMINO-ACID SEQUENCE OF ACTH and "B" (PIG)
(HARRIS AND LERNER, 1957)

| Species | "B" |
|---|---|
| Human .. .. .. | 7 i.u./mg. |
| Ox (I.S.) .. .. .. | 2 " |
| Horse .. .. .. | 5 " |
| Sheep .. .. .. | 1 " |
| Pig .. .. .. .. | 10 " |

amount of "B" activity in extracts of the posterior lobe of the pituitaries of certain species. The values for "B" in extracts of ox and pig glands probably represent the maximum amount present since these glands were obtained almost immediately after death. The activity stated for the other glands is probably low since they were obtained some time after

killing the animal and "B" activity quickly disappears. Since "B" is so widespread and occurs in such amounts in the animal kingdom, it probably has some function in mammals.

In the ox and pig the gland is easily divisible at the hypophyseal cleft but the intermediate lobe is inseparable from the posterior lobe. The cells of the intermediate lobe are said to be responsible for "B" production. In man, however, this is not so. In fœtal life there is a layer of cells which resemble the intermediate lobe but it disappears in early life and we are left with areas of "basophil-cell invasion". In the rat similar basophil cells in the anterior lobe are believed to produce ACTH. Since "B" and ACTH are similar chemically, the areas of "basophil-cell invasion" may be responsible for "B" production in the human. However, our own evidence is that the anterior lobe of the human gland contains on a weight basis as much as the areas of "basophil-cell invasion" (Morris *et al.*, 1956).

The fact that the human gland contains such a large amount of "B" leads us to wonder if it has some significant function about which we know nothing, or if it is a "brick" used in the building of a more complex polypeptide. If we compare the structures of ACTH and "B" we see a heptapeptide present in both. If the lysine and serine in "B" were changed

TABLE III

| | .. | .. | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | .. | .. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACTH | .. | .. | Tyr. | Ser. | Met. | Glu. | His. | Phe. | Arg. | Try. | Gly. | Lys. | Pro. | .. | .. |
| "B" | .. | .. | Tyr. | Lys. | Met. | Glu. | His. | Phe. | Arg. | Try. | Gly. | Ser. | Pro. | .. | .. |
| | .. | .. | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | .. | .. |

then there would be eleven amino acids which would be similar, and it may be that the simpler "B" molecule or part of it is used for the building of the more complex 39 amino-acid ACTH.

The various ACTH preparations used in clinical medicine are made from either ox or pig glands and each sample contains large amounts of "B" which could be partly intrinsic to the ACTH molecule but largely due to contamination.

As well as estimating the "B" activity in extracts of pituitary glands we have also attempted without success to measure the amount of "B" in blood and urine. Our test, using xenopus, is probably not sensitive enough since there is probably less than 0·01 i.u. per 100 ml. of blood. There have been many claims that there is an increase in "B" in blood in many diseases but you cannot be certain that the substance being measured is "B". Before you can state that it is "B" three criteria must be fulfilled:

(1) The substance must produce expansion of melanophores in the intact animal.
(2) The substance must produce expansion of melanophores in the hypophysectomized animal.
(3) The substance must emanate from the pituitary.

We know that many amines such as adrenaline, phenylalkylamines, &c., cause darkening in amphibia and it is possible that similar substances may be extracted and cause the darkening effect.

In pregnancy, too, the estimation of a darkening substance in the urine is used in the Konsuloff (1934) test when the test animal is *Rana esculenta*. If you use xenopus as the test animal you find darkening in a small percentage of cases only. In one sample of 105 known pregnancies only 10 gave a positive effect on melanophores of xenopus (Hobson, 1958). This substance was claimed to be "B" but it does not satisfy the three criteria stated above and it is unlikely that it is "B".

We have injected subcutaneously large doses of "B" into rabbits but failed to extract any "B" from the urine. Even if injected i.v. the "B" content of blood is only high for a short period of time. So it does seem that the darkening effect reported by many workers is not specifically due to "B" and until we isolate either one or more of these substances from urine we cannot be sure of either their chemical nature or their source.

## REFERENCES

HARRIS, J. I., and ROOS, P. (1956) *Nature, Lond.*, **178**, 90.
——, and LERNER, A. B. (1957) *Nature, Lond.*, **179**, 1346.
HOBSON, B. M. (1958) Unpublished.
HOGBEN, L., and GORDON, C. (1930) *J. exp. Biol.*, **7**, 286.
——, and SLOME, D. (1931) *Proc. roy. Soc.*, Ser. B., **108**, 10.
KONSULOFF, S. (1934) *Klin. Wschr.*, **13**, 776.
LANDGREBE, F. W., and MITCHELL, G. M. (1954) *Quart. J. exp. Physiol.*, **39**, 11.
MORRIS, C. J. O. R., RUSSELL, D. S., LANDGREBE, F. W., and MITCHELL, G. M. (1956) *J. Endocrin.*, 13, 263.

## BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

**Davidson (M.).** Memoirs of a golden age. pp. 140. Oxford: Blackwell. 18s. 0d. 1958.

**Dimitrov-Szokodi (D.).** Die chirurgische Behandlung des Bronchialasthmas. pp. 143. Berlin: Volk u. Gesundheit. DM. 24. 1957.

**Ferreira (L. E.).** A ressecção escleral lamelar do descolamento da retina. Brasil: Estado do Rio, Niteroi. pp. 191. 1956.

**Franke (H.), and Schroeder (J. H.).** Die Würzburger Medizinische Universitäts-Poliklinik 1807–1957. pp. 123. Stuttgart: Thieme. 1957.

**Hainzl (H.).** Chirurgie der Hand- und Armverletzungen. pp. 413. Berlin: Volk u. Gesundheit. DM. 41. 1957.

**Hegglin (R.).** Differentialdiagnose innerer Krankheiten. 4th edit. pp. 678. Stuttgart: Thieme. 1956.

**Higgins (T. Twistington).** Alexander Simpson Smith 1900–1942. pp. 30. Jersey: printed by Bigwoods. 1957.

**Hoff (F.).** Behandlung innerer Krankheiten: richtlinien und Ratschläge für Studierende und Ärzte. 7th edit. pp. 653. Stuttgart: Thieme. DM. 57. 1956.

**Jochheim (K.-A.).** Grundlagen der Rehabilitation in der Bundesrepublik Deutschland. pp. 203. Stuttgart: Thieme. 1958.

**Klyueva (N. G.), and Roskin (G. I.).** Problema protivorakovykh Antibiotikov. pp. 247. Moscow: Institute of Albumins and Vaccines. 1957. (Two copies.)

**Lastres (J. B.).** Daniel A. Carrión. pp. 146. Lima: Editorial San Marcos. 1957.

**Moutier (F.).** L'Aphasie de Broca. pp. 774. Paris: Steinheil. 1908.

**Nonidez (J. F.), and Windle (W. F.).** Textbook of histology. pp. 456. New York: McGraw-Hill. 40s. 6d. 1949.

**Olivier (C.).** Maladies des veines: diagnostic et traitement. pp. 599. Paris: Masson. 1957.

**Royal College of Physicians of London.** Committee on Electroencephalography. (Revised) report, January 1958. pp. 7. London: R.C.P. 1958.

**Royal College of Physicians of London.** Rheumatic Fever Committee. Further report, July 1957. pp. 12. London: R.C.P. 1957.

**Savill (A. F.).** Alexander the Great and his time. 2nd edit. pp. 300. London: Rockliff. 1956.

**Slovenská Akadémia Vied.** Klinická problematika niektorých kostných novotvarov. pp. 327. Bratislava: Slovenská Akad. Vied. 1957.

**Walker (K. M.), and Strauss (E. B.).** Sexual disorders in the male. pp. 248. London: Hamish Hamilton. 1939 (reprinted 1942).

**Washington, D.C.: Government Hospital for the Insane.** Centennial papers, Saint Elizabeth's Hospital, 1855–1955. pp. 251. Washington: St. Elizabeth's Hospital. 1956.

**Weber (F. Parkes).** Medical teleology and miscellaneous subjects. pp. 86. London: Lewis. 15s. 0d. 1958.

**Wellcome Foundation Ltd.** The Wellcome Museum of Medical Science. pp. 39. London: Wellcome Foundation. 1958.

**White (M. M.).** Womanhood. pp. 107. London etc.: Cassell. 1947.

**Zilberberg (B.).** Pênfigo e dermatite de Duhring-Brocq: contribuicão para o seu estudo histocitológico. (English summary.) pp. 175. São Paulo: Univ. 1955.

# Section of General Practice

President—G. M. KERR, M.B., L.R.C.P., F.F.A.R.C.S.

[*March* 19, 1958]

## DISCUSSION: AN APPRAISAL OF HYPNOTISM IN GENERAL PRACTICE

**Dr. H. Stewart** (Watford): I decided to use hypnotism when orthodox therapies had failed me in dealing with my practice quota of chronic sick patients.

I do not want to go into the methods of trance induction nor relate the various phenomena that can be obtained in the hypnotic trance, but a few facts must be stated here. Firstly, 90% of the patients that one tries to hypnotize can be hypnotized when one is competent. The remaining 10% will probably be able to be hypnotized by another therapist. Secondly, of that 90%, 35% will go into a slight trance, 35% into a medium trance and 20% into a deep somnambulistic trance. For most of our therapy a deep trance is not required and so it is clear that the use of hypnosis will extend over most of our patients. However, it must be noted that, in general, the deeper the trance, the greater is the range of hypnotic techniques available for use in therapy. These may be roughly divided as follows:

(1) *Simple suggestion:* All doctors use suggestion when treating patients. We tell them that they will feel better and that their pains will go if they drink this medicine, that their skin eruption will heal if they apply this ointment, &c. Suggestion during the hypnotic trance is a very powerful tool and can be used for symptom removal. Thus when the symptoms are gone, the patient is pronounced cured and as symptom removal can be used on any disease, all diseases become curable by hypnotic suggestion. Unfortunately if the underlying pathological state, whether an organic lesion or an emotional conflict, is not also resolved, the symptoms usually return in the same or a different guise. It behoves us to ponder every time we remove a sympton and think of the possible consequences.

(2) *Educative:* A patient can be taught how to remove symptoms for himself. This is achieved by teaching him autohypnosis, a method based on the phenomenon known as post-hypnotic suggestion. I shall mention this in more detail later as autorelaxation.

(3) *Removal of inhibitions:* It is often found when dealing with psychogenic disturbances that when the patient is asked "Is anything worrying or disturbing you?", the answer is in the negative. If the patient is then hypnotized and the question repeated, one often finds a flood of material is released. Thus some resistant force has been overcome during the process of hypnosis and the patient is able to talk. It is also interesting to notice that if a patient does talk without hypnosis, it is often with no trace of emotion. In a trance, the emotional affect of the words is also released.

An extension of this to the extreme is the:

(4) *Obtaining of emotional abreactions:* This occurs when some past emotionally-repressed terrifying experience is re-lived during a trance. This technique is particularly useful in emotional disorders that can be pin-pointed to date from such an experience, e.g. being involved in a bad accident, the bursting of a shell or bomb near by. It is with this technique that rapid dramatic cures are made.

(5) *Regressions and hypno-analysis:* Regressions occur almost always only in deep trance patients and are manifested by the patient assuming the chronological age suggested by the hypnotist and acting as though he were that age. The important feature is that the memories of that age are all brought to the surface and provide a valuable analytic tool when conducting a hypno-analysis. This is an investigation of the psychodynamics of the patient while in a hypnotic trance and in general, the deeper the trance state, the more effective can be the analysis. But this is a dangerous field for the doctor unless he can handle the material produced with the necessary interpretative insight.

### CONDITIONS SUITABLE FOR HYPNOTHERAPY

The disorders in which hypnotherapy is likely to be effective fall into three main categories: (1) psychosomatic, (2) psychoneurotic, (3) organic with anxiety-tension overlay.

*Psychosomatic disorders.*—These may be regarded as conversion symptoms of an underlying emotional conflict manifesting themselves as organic bodily changes. In this group are the asthmas, eczemas, migraine, various gastro-intestinal disorders, &c. It is in this group that hypnotherapy is of great value, since it allows of direct symptom removal together with the means of tackling the emotional conflict. However, direct sympton removal alone sometimes cures without a reconversion of symptoms, e.g. asthma being replaced by eczema

or migraine. Nevertheless it is always wisest to do both since this will give the greatest probability of cure.

I shall use asthma an an example of this treatment. A trance is induced and the patient asked to talk of anything that worries him. If material is produced, it is worked through with the patient during this and subsequent sessions and the patient helped to see his conflicts in the clearest possible light. Towards the end of the session it is suggested that the patient will improve week by week (to suggest immediate cure is too much for him to accept), that his attacks will get less violent and less frequent and that you will teach him to control an attack by himself: this is done by teaching him auto-relaxation. It is suggested that if he feels an attack is impending, he should slowly relax his body from the feet upwards as he does when a trance is induced, and that as he relaxes, the attack will pass off. These suggestions are repeated three or four times and the trance is then ended.

*Psychoneurotic disorders.*—Under this heading are the two important groups of anxiety states and conversion hysterias. Of the anxiety states, the severe case is very difficult to tackle without psychotherapeutic training and I would suggest that they should not be tackled in practice. Obsessional neuroses are also very difficult and treatment should not be attempted.

Hypnosis with psychotherapy has an advantage over orthodox psychotherapy in that highly charged emotional material can be brought to light far more rapidly in a good hypnotic subject. The best example of this is in the emotional abreaction that may often be obtained in the conversion hysterias and which can only be obtained in orthodox techniques by using special abreactive agents, e.g. Pentothal, ether or carbon dioxide. Nevertheless one must be prepared for many long and difficult sessions.

One factor worthy of notice is that the dependence of the patient on the hypnotist is no greater than that occurring in orthodox therapy.

*Organic disorders.*—We often see patients with some organic disorder—cardiac, pulmonary, nervous or skeletal in origin—whose disabling symptoms do not appear to be accounted for by the actual organic lesions present. One then describes them as having a functional overlay of anxiety causing muscular tension and rigidity. In this type of case, the anxieties are investigated as in any other and the patients given suggestions for symptom-removal and auto-relaxation. The results are often very gratifying but it should be remembered that the disease process is not cured—only the symptoms and anxieties are removed.

Hypnosis may also be used as anæsthesia and analgesia in surgery and midwifery; to stop excessive cigarette smoking, nail-biting and thumb-sucking, and to reduce weight in obesity. In midwifery it can be used to make the patient relaxed, to relieve fear, and if a good subject, to obtain complete analgesia. In the same way it can be used in general practice minor surgery. Its powerful suggestive qualities are of course valuable in stopping "bad habits" but it must be admitted that results are not as good as they might be for unless the psychic basis of the habit is removed, they do tend to relapse.

*Disadvantages.*—There seem to be no real disadvantages in the use of hypnosis provided that one does not become too ambitious in the scope of treatment. However, there is so much that can be done, that its limitations are of no great importance. Its ultimate value will really be decided by the general practitioner who has the patient's complete medical history and can therefore assess the results of any particular therapy.

**Dr. A. A. Mason** (Dept. of Psychiatry, West London Hospital): Before discussing the uses of hypnosis it is necessary to explain certain facts in its chequered past.

Both the doctor practising hypnosis and the patient receiving it have played a part in the waxing and waning of its popularity. The patient usually suffers from a chronic illness either organic or psychogenic which has not responded to orthodox therapy. This patient also blames the doctor for his failure to get well instead of realizing that medicine as a whole has limitations which have to be accepted, and he feels that somewhere there exists someone who knows of a cure for him. He will try specialist after specialist and after the orthodox practitioners have been exhausted he will try the unorthodox with all their rays, boxes and currents. Of course, these patients are really looking for magic and if anyone searches for magic in any field he will always find someone willing to supply it, heavily and expensively disguised in scientific jargon. Hypnosis has been used in just this way all too frequently with the result that any possible good or usefulness is overlaid by dramatic and overstated claims. A low percentage cure rate obviously divests magic of much of its magic, and so to maintain his omnipotence the magician has to exaggerate his success and lose and minimize his failures. The rest of the medical profession, quickly discerning the gross exaggeration, will then reject the claims entirely and so lose sight of the genuine cures, few though they may be.

The motives of the hypnotist are more complex and range from the frank charlatan—who cares nothing for results but supplies hypnosis because there is a ready market—to the enthusiast who constantly seeks new cures, applying them with great fervour. It is

the personality of the latter rather than what he uses which produces the results, and though his immediate cure rate is high his relapse rate is also high but is rarely published.

Then there are the doctors, often professional failures, who use hypnosis to give themselves a sense of power and grandiosity which compensates for their inadequacy. The combination of the magic-searching patient and this type of practitioner produces these large up-and-down swings in the popularity and employment of hypnotism. The up-swings are due to fantastic cure claims—the cures being sometimes a temporary relief of real organic symptoms by hope and enthusiasm, and sometimes conversion of neurotic symptoms which appear as physical lesions. The down-swings by relapse, disillusionment and finally denouncement by the profession, and the large numbers of cures—as at a faith healing meeting—which vanish in the morning. The small number of real therapeutic gains unhappily are also swept away in the generalized denouncement.

The last naturally occurring down-swing in hypnosis one hundred years ago swung deeper than ever because of the discovery of general anæsthesia which took hypnosis out of the anæsthetic field, and the abandonment by Freud of hypnosis as a method of exploration of the unconscious in favour of the free association techniques.

To-day there is an up-swing in the popularity of hypnotism once more and it is to be hoped that the assessment of value this time will not be left to magicians and psychopaths but that reputable medical centres will play a major part in its evaluation.

The production of hypnosis depends upon a technique which is simple to learn. It requires no special ability or power. There is certainly no necessity for specialists or special clinics and the G.P. is as well suited to use it as anyone.

Hypnosis can be applied to a large proportion of people, probably 80–90%, and the techniques of production of the hypnotic state are all basically similar and consist of repeated rhythmical, monotonous, sensory stimulation. The sensory stimulation can be auditory, visual or tactile. The somnolence produced by the rocking and noise of a train, by the lecturer who drones on and on, by the barber or masseur, is undoubtedly a hypnoidal state. The crooning mother rocking her baby, the rocking of a hammock or the sea, music with a monotonous beat, all produce sleepy, trance-like hypnotic states. All these ways of producing a trance are followed closely by the hypnotist, who stimulates rhythmically and monotonously, until, bored and fatigued, the patient drowsily passes into a slumber.

The hypnotic state is of no value in itself, but certain well-recognized phenomena occur or can be made to occur in this state. Suggestions of numbness and absence of pain will bring about varying degrees of analgesia by a true raising of the pain threshold. This phenomenon as shown by EEG examination approximates to what happens under general analgesia, and pain impulses are diverted from the cortex to the reticular system and thalamus.

The degree to which this happens varies and is related to the depth of trance which has been reached. In a deep trance a considerable degree of analgesia can be produced and many major operations (Mason, 1955*b*, 1956; Kroger and DeLee, 1943, 1957) have been performed. There are no toxic effects of anæsthetic drugs, shock is minimized and this is obviously an ideal anæsthetic for the poor-risk patient. However, not more than one in five people can enter such a trance and therefore the use of hypnosis for major surgery will never be more than a curiosity except in very special circumstances.

In a medium trance which can be reached in approximately 35% of cases some analgesia is present although not enough for major surgical procedures. Taking together deep and medium trance patients one finds that in over half of one's patients some degree, sometimes considerable, of analgesia can be achieved. This is extremely useful in minor surgical procedures and for instrumentation, which may not be painful but can cause considerable discomfort especially in the very sick, the young and the apprehensive. Dental fillings, lumbar punctures, urethral and rectal instrumentation, antral puncture, changing painful dressings, burns and mastoid (Crasilneck *et al.*, 1955), orthopædic and physiotherapeutic manipulation of painful joints and a host of other procedures too trivial for general analgesia and not suitable for local injection, can be comfortably performed in the hypnotic state.

In the light trance state into which approximately 35% of people can go, there is no analgesia present but even here hypnosis can be useful as a premedication for general anæsthesia in children, as an adjunct to local anæsthesia and generally speaking to remove the psychological overlay of pain. The patient who continues to feel pain despite adequate local analgesia is eminently suitable. Hypnotism is specially useful in the casualty department. Fractures and dislocations can be effectively reduced and when the patient has a full stomach he can be treated immediately and so avoid undue waiting and pain.

Again in childbirth the use of hypnosis is rewarding. It is the only anæsthetic which is powerful enough to produce a painfree labour without detriment to the mechanics of the labour or the infant's respiratory efforts. There is no time limit to its action, and no apparatus or specialist is needed to apply it. DeLee (1955), Michael (1952) and Perchard (1955) have all written favourably on its use in this field.

Hypnosis is also of value in the pain caused by disease processes as distinct from surgical procedures. The pains of trigeminal neuralgia, causalgia, post-herpetic neuralgia and phantom limb can sometimes be treated remarkably effectively by the use of hypnosis in two ways. Firstly, the number and severity of attacks can be cut down by direct suggestion in the hypnotic state. Secondly, the pain of attacks can be relieved by the patient himself utilizing autohypnosis. Butler (1954) has reported favourably on pain relief produced in inoperable cancer, hypnosis enabling drugs to be withheld for a considerable time and potentiating the drugs when they were needed, sometimes even obviating their use.

Direct suggestion aimed at symptom removal is sometimes useful in that conglomeration of diseases which for want of a better term are called psychosomatic. Chronic skin disorders, especially of the pruritic variety have been helped effectively. Gordon and Cohen (1952) have reported on over 130 chronic skin disorders treated with about a 60% recovery rate after a four-year follow-up. I myself have treated 61 similar cases with 28 successes which still remain clear. Of particular interest in the skin field is the treatment of warts of all varieties. These are notoriously amenable to suggestion—but I have a series of 23 with 21 recoveries, all of whom had had extensive treatment previously, including suggestion of various kinds. Even a case of congenital icthyosis has responded (Mason, 1952, 1955*a*). Multiple warts of the nail beds and plane warts of the face obviously lend themselves to this innocuous form of removal.

Asthma, that most fickle of all conditions, has been treated extensively by hypnosis by many practitioners. My own results are less good than Dr. Stewart's (1957) but nevertheless one-half of the patients I have treated seem to have benefited considerably and I have not noticed any tendency to convert to eczema. One case treated became clinically clear while remaining serologically unchanged (Mason and Black, 1958) where asthma developed late in life and I suspect that many of these cases cover psychoses and the asthma is perhaps preferable to what would emerge were it to go.

Gastrointestinal conditions like globus hystericus, hysterical vomiting, water-brash, mucous and ulcerative colitis have all been helped by the use of hypnosis and certainly it is worth trying before surgery is resorted to in the latter condition.

As far as the genito-urinary tract is concerned, I have found that dysmenorrhœa and enuresis respond very favourably while conditions like frigidity, dyspareunia, premature ejaculation and impotence hardly respond at all.

Certain troublesome habits like nail biting, thumb sucking, persistent hiccup, cigarette smoking and overeating have all been treated with some success by the use of hypnosis. When the addiction is severe, however, like alcoholism or gross obesity simple measures like hypnosis are not sufficient and psychotherapy is usually necessary.

It is interesting to speculate as to why these psychosomatic disorders, which undoubtedly cover neurotic conditions, should get well at all by the use of hypnosis and it is possible that the answer lies to some extent in the severity or otherwise of the underlying conditions.

Probably the symptom which covers a mild neurotic condition responds quite well to the use of hypnotic suggestions and the released anxiety or conflict emerges and is then dealt with in the therapeutic sessions. The patient in the first place has displaced his conflict say into his skin: you then reverse the process and bring it back and force him with your help to face it and deal with it. It is also probable that if the psychosomatic condition covers something more severe than a mild neurotic condition it will not be shifted by a process as superficial as hypnotic suggestion, for we do not see psychotic or major psychoneurotic breakdown in any numbers following this treatment. I have had only three psychotic episodes following the treatment of some 300 cases in the last four years, a figure not significantly greater than the normal expectancy.

In psychiatry, following the abandonment by Freud early in his work, hypnosis has come full circle and is now increasingly used among psychiatrists in certain well-defined conditions. We search all the time for methods which will assist us to help the ever-increasing numbers of patients we have to treat and undoubtedly hypnosis helps in many, from simple direct suggestive techniques for chronic hysterics and delusional hypochondriacs, to the complicated year-long procedures like the hypno-analytical techniques described by Wolberg. In a recent nation-wide survey in the U.S.A. among the many therapeutists who utilize hypnosis not one could testify that dangers exist which would discourage its employment by trained professional persons. The consensus of opinion amongst them was that hypnosis is valuable in all types of psychotherapy, palliative and reconstructive. It was Freud (1955) himself in 1919 who said: "It is very probable too that the large-scale application of our therapy will compel us to alloy the pure gold of analysis freely with the copper of direct suggestion and hypnotic influence too."

Summing up, one can justifiably say that undoubtedly the longer techniques of psychoanalysis and psychotherapy are better for severe conditions but in short-term and more limited procedures hypnosis is often valuable.

REFERENCES

BUTLER, B. (1954) *Cancer, N.Y.*, **7**, 1.
CRASILNECK, H. B., *et al.* (1955) *J. Amer. med. Ass.*, **158**, 103.
DELEE, S. T. (1955) *J. Amer. med. Ass.*, **159**, 750.
FREUD, S. (1955) Collected Papers. Ed. J. Strachey. London; Vol. **17** (1917-19).
GORDON, H., and COHEN, K. (1952) *Int. derm. Congr.*, **X**, p. 376.
KROGER, W. S., and DELEE, S. T. (1943) *Amer. J. Obstet. Gynec.*, **46**, 655.
——, —— (1957) *J. Amer. med. Ass.*, **163**, 442.
MASON, A. A. (1952) *Brit. med. J.*, ii, 422; (1955*a*) *Brit. med. J.*, ii, 57; (1955*b*) *Anæsthesia*, **10**, 295; (1956) *Proc. R. Soc. Med.*, **49**, 481.
—— , and BLACK, S. (1958) *Lancet*, i, 877.
MICHAEL, A. M. (1952) *Brit. med. J.*, i, 734.
PERCHARD, S. D. (1955) *Proc. dent. med. Soc. Study Hypnosis*, **3**, November.
STEWART, H. (1957) *Brit. med. J.*, i, 1320.

**Dr. C. A. H. Watts** (Ibstock, Leicester): My introduction to hypnotism was perhaps a little unfortunate. The subject interested me, and when in the Army I was sent on a psychiatric course, I thought that I might see some patients hypnotized. However hypnotism was never used and when I asked some of the psychiatrists to demonstrate it to me, like the wedding guests of the Bible " all with one consent began to make excuse". I could find no one who would help me and so I decided I would have to teach myself the art. For some years I used hypnotism occasionally, in some cases with considerable success, and yet in the end I gave it up. I propose to outline why I now feel reluctant to use it as a general practitioner.

Reading the literature we can see how wide a range of illnesses can be benefited by this type of treatment: asthma, enuresis and habits such as smoking and alcoholism, as well as a vast selection of psychiatric disorders. Many of the diseases are intractable and troublesome to general practitioners and specialists alike. If hypnotism is so effective and so safe, why is it not widely used by the profession as a whole? Mesmer appears to have first described it and made use of it in the 18th century, although I have no doubt that it had been used by various people since the dawn of history. It has never been a monopoly of the medical profession. A few medical pioneers like James Esdaile used it to produce anæsthesia before the discovery of chloroform and ether. On the other hand most surgeons preferred the rum bottle and operative speed to the hazards of hypnosis. Why has such a promising weapon not taken on with the profession although it has been known and practised in a desultory manner for at last 200 years?

To practise the art successfully one must have the right type of patient. It was because hypnosis did not work on some of his cases that Freud abandoned it as a routine practice. Strauss (1951) suggests that 90% of people are susceptible to light hypnosis, some 40% to deep hypnosis but only 10 to 15% can reach the hypnotic coma in which surgical operations can be performed. Hypnotists claim that once a patient has been put out a few times by hypnosis, he can be sent into such a state very rapidly on subsequent occasions. It is obvious that some patients enjoy that situation. They seem to get some subtle satisfaction from the procedure. I feel sure that these patients are the exception and not the rule, and the majority of people are put off by the idea of submitting to hypnotism. In the days before hypnotism was banned as a form of public entertainment, a variety hypnotist came to give a show in our village. One mother told her small daughter that she was going to see him. " Don't go Mummy ", the little girl pleaded. " He fastens your hands above your head and you cannot get them down." That child's fear of the process is I feel the fear of many.

The uncertainty of hypnosis and the mystery of its mode of action are disadvantages. Even the hypnotist is often ignorant of why his patient responds. Dr. A. Fry (1958) told me how he had cured a woman of very troublesome pruritus ani which had not responded to other forms of treatment. It was a very gratifying result and one can see to a point what had happened. He had stopped the compulsive scratching and that allowed the skin to heal. Later the same patient came along with herpes zoster. It was extremely painful and she was just going for her holidays. He hypnotized her again and the pain went. Neither he nor anyone else can explain this. One can argue that no one knows how E.C.T. works, and yet many of us make good use of the treatment. I feel that the difference is that we can be quite certain that if we apply the current the patient will have a fit and that this result will be achieved each time we press the button. In dramatic forms of treatment if the patient fails to respond, one can be in difficulty. The treatment may be blamed for the head noises or the defective memory. If it has been given by a specialist in some remote hospital, the general practitioner can still support the patient. Both can project their disappointment on to the psychiatrist. This cannot be done if the family doctor has given the treatment himself. It is comparable with a case of failed forceps. Both are an unpleasant experience for the conscientious general practitioner who is left with a very uneasy conscience because there has been an error of judgment.

Even more important than the type of patient is the type of doctor, and this to my mind is the main reason why hypnosis has not taken on. Only a very small proportion of medical men or women can stare confidently into their patients' eyes telling them " Your eyelids are becoming heavy, very heavy, you are feeling sleepy, very sleepy " and so on. It is embarrassing when I become aware that the patient is one of the large group of resistive people. He remains aggressively wide awake, mildly amused at my antics. A general practitioner lives very close to his patients and he has to be approachable and available to help them in all manner of mental and physical illnesses. He cannot afford any unnecessary barriers of misunderstanding. Soon after I had settled in Ibstock I realized that I was becoming labelled as interested in " nerves ". I began to realize that working as a country doctor there were certain lines of treatment and attitudes of mind which were rather upsetting to some patients, and hypnotism was among them.

On theoretical grounds hypnosis should be most useful in the hysterical type of case, as one of the characteristics of hysteria is suggestibility. Kennedy (1957) listed conditions in which hypnosis is often the treatment of choice. These included fugue, hysterical stupor, hysterical deafness, aphonia and various other hysterical conditions. These frankly hysterical episodes are actually very rare in general practice. In twelve years I have only had one fugue, one aphonia and one case of blindness. I have had no cases of deafness. In each instance the situation was handled without resort to hypnosis. In one case I was called out to the modern school because a child had collapsed on his way to the bus. I found a boy of 12 lying on a couch with several members of the staff standing by looking anxious and worried. A physical examination of the lad showed no evidence of any serious cause for his stupor. He resisted all attempts to open his eyes and I felt that he was in a hysterical state. The situation was embarrassing; he had to be taken home and the school was closing. I gave him 1·0 c.c. of sterile water intradermally raising a wheal, and I told the staff very clearly that if he did not improve in five minutes I would have to give him another injection. Shortly afterwards he opened his eyes and said that he was much better.

A case of fugue had me out of bed at 2.0 a.m. He had been found wandering and lost by the police. When I went into this case thoroughly I decided the basis of his trouble was endogenous depression, and E.C.T. was the treatment of choice.

Medical hypnotists do not of course confine their attention to the hysterical type of patient. They apply their art on many psychoneuroses and psychosomatic conditions such as asthma and dermatoses. Hypnosis is not used just to remove the symptom, but wherever possible relevant psychopathology is uncovered, and quite often the patient is abreacted. I feel that as a rule there are simpler methods of dealing with the type of case we meet with in general practice. With psychotherapy at a conscious level the problem can usually be solved, without resorting to the mumbo-jumbo of hypnotism. The advocates of hypnosis argue that they get at the root of the problem more quickly. Speed is not always an advantage in psychological treatment and in any case hypnotism itself is time-consuming. Stewart (1957) states that his patients were seen 8 to 10 times at weekly intervals for 30- to 50-minute sessions; that is, a case will take four to eight hours in all. This surely is no short cut to recovery. I rarely take more than three hours over my cases. If in the course of psychotherapy I reach a resistance which I cannot get around, I feel two courses are open. The case may be sent to a psychiatrist who is in sympathy with my methods of treatment with full notes as to what has happened. He can usually suggest a new line of approach to the problem. If this seems inappropriate for some reason, there are cases in which narco-analysis can be used. I am not at all keen on this procedure at general practice level but I feel that it is much more predictable than hypnosis. From the point of view of the doctor the patient is certain to go under the influence of the drug, and the patient is left with the knowledge that between him and the doctor is a syringe. He cannot be influenced by some formula. He readily accepts in these days that everyone can reasonably be expected to be influenced by drugs and there is no suggestion of any alarming or occult domination of mind by mind. His general practitioner remains for him a normal individual who can be consulted on any of his every day ills and is in no danger of becoming a magician.

For these reasons I am not myself keen on the practice of hypnotism in general practice. There are, however, good medical hypnotists in the ranks of general practitioners, and they can sometimes help people when we have failed to do so. I feel that if the general practitioner cannot help his patients by a form of psychotherapy which can be performed with his patient sitting on a chair in the consulting room then the case should be passed on to the psychiatrist. While I am all for the general practitioner taking his full share of the load in psychiatry, it is a wise man who knows his own limitations.

REFERENCES

Fry, A. (1958) Personal communication.
Kennedy, A. (1957) *Brit. med. J.*, i, 1317.
Stewart, H. (1957) *Brit. med. J.*, i, 1320.
Strauss, E. B. (1951) In: British Encyclopedia of Medical Practice. London; Vol. 7, p. 1.

# Section of Comparative Medicine

President—J. B. Brooksby, D.Sc., Ph.D., M.R.C.V.S.

[*March* 19, 1958]

## DISCUSSION ON COMPARISON OF DISORDERS OF THE INTERVERTEBRAL DISC IN MAN AND ANIMALS

**Mr. D. D. Lawson** (Glasgow):

*Intervertebral Disc Protrusion in the Dog*

Intervertebral disc protrusion in the dog has been recognized for approximately the past decade (Olsson, 1951; Hansen, 1951; Olsson and Hansen, 1952) but the clinical symptoms associated with this condition have been known for a very long time.

As long ago as 1896 Dexler reported the pathological features of "enchondrosis intervertebralis" of dachshunds which had been paralysed. He did not, however, consider that these "chondromas" were in fact disc protrusions and this fact was not recognized for more than fifty years.

A factor which has contributed to some extent to the confusion on this subject has been the very wide range of symptoms that the affected dogs may exhibit.

The intervertebral disc in the dog, like that in man, is composed of two parts—the central nucleus pulposus, which is gelatinous and is surrounded by the annulus fibrosus, the peripheral lamellated portion, which is much thicker ventrally than dorsally.

The 7th–15th discs are also covered dorsally by the conjugal ligaments which join the heads of the 2nd–10th pairs of ribs. These conjugal ligaments largely replace the dorsal annulus in this area and would appear to be responsible for the remarkable lack of protrusions in this area (Fig. 1).

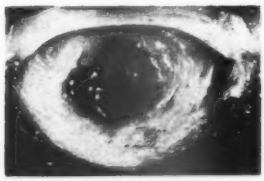


Fig. 1.—Transverse section of ninth intervertebral disc of dog to show well-developed conjugal ligament.

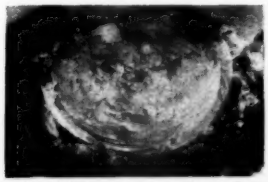


Fig. 2.—Transverse section of grossly degenerate lumbar intervertebral disc of dog to show gross Type I protrusion.

Degeneration of the nucleus pulposus would appear to be a prerequisite for the subsequent development of a disc protrusion. The normally gelatinous nucleus becomes firm: chondroid, calcified or dry and crumbly.

Following this degeneration there is a tendency for faults to develop in the annulus. These develop along tortuous tracts and finally the nuclear material breaks through to form a disc protrusion (Fig. 2).

This form has been classified by Hansen as Type I (protrusion)—these present as major features (i) large size (up to $15 \times 10 \times 5$ mm. or more), (ii) degenerate nuclear material free in the spinal canal, (iii) identifiable tracts running through the annulus, and (iv) adhesions to the spinal dura mater occurring fairly frequently. These are commonly associated with severe symptoms.

There is another type of protrusion—Hansen's Type II—in which the masses are smaller, and where the annulus is bulged rather than broken through. There is seldom any dural adhesion.

These protrusions occur dorsally and lie into the spinal canal and cause spinal cord pressure. Because of this and because of the location of protrusions in two groups, cervical and thoracolumbar, very wide variations in signs occur. The degree of affection is also associated with the degree of cord compression and the rate at which the protrusion develops (Olsson's dynamic factor).

*The Clinical Features*

Disc protrusion cases may be divided on an anatomical basis into two main groups, cervical and thoracolumbar.

*The cervical protrusion* cases exhibit especially pain with rigidity of the neck and spasm of the cervical muscles (fibrillation). These animals are often very apprehensive and will

frequently scream without having been touched. Brachial paralysis occurs in some cases. Very rarely quadriplegia occurs. Pain tends to be persistent in these cases.

*The thoracolumbar* cases show much more variation and may be subdivided into a series of groups:

(1) Cases which show *pain* only; the dog appears dull, stands with back arched and is disinclined to move. These are fairly unusual and may in many ways resemble cases of cervical protrusion.

(2) Cases with *pain and paresis;* similar to the first but with additional loss of control of hind-legs.

(3) *Paraplegics*, in which control of hind-legs is completely lost, and the legs are either dragged behind when the dog moves ("flaccid paraplegia") or held in extension ("spastic paraplegia"). These cases frequently show lumbar pain for the first twenty-four to forty-eight hours of affection. The rate of onset may be sudden and dramatic or may develop slowly over three or four days. The flexor and extensor reflexes are present in the hind-legs, but no weight-bearing reflexes can be elicited. Tail movements are present. Urine is frequently not passed normally, but only when the bladder is distended. In a very few cases marked wasting of the posterior half of the body occurs and if this happens the dog always dies after some three to four months.

(4) *Absolute paralysis:* these cases start like the typical paraplegics but soon show (*a*) marked posterior cord irritability, shown by marked muscle jerk of the hind-legs on the slightest skin stimulation. This is followed by (*b*) complete loss of all reflexes and of all muscle tone in the hind-legs. This may co-exist with ascending paralysis or may occur alone. The spinal cord in these cases has undergone a liquefactive necrosis and recovery is impossible.

(5) *Acute ascending paralysis;* these cases start like the typical paraplegias, but rapidly deteriorate to the state where the animal lies on its side and yelps. Death ensues within approximately forty-eight hours. Some cases may be less severe and may survive up to seven to ten days; these show a markedly raised head position and a Schiff-Sherrington phenomenon.

*Radiographic Diagnosis*

Because of the fairly frequent occurrence of calcification in the disc of the dog, disc protrusions may in many cases be visualized on a plain film. These can often be seen in the intervertebral foramen on a lateral projection (Fig. 3). Calcification of the nucleus of the



FIG. 3.—Radiograph of lumbar spine to show gross calcified intervertebral disc protrusion which virtually occludes the intervertebral foramen.

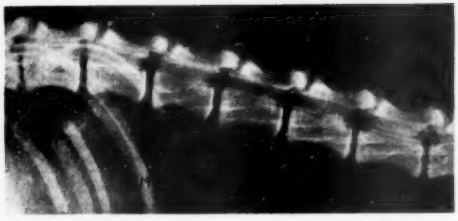


FIG. 4.—Radiograph of lumbar spine to show passage of contrast agent over gross calcified disc protrusion.

disc itself, *in situ*, is only indicative of disc degeneration. Diminution of the disc space is suggestive that there has been loss of disc substance, but is not of itself conclusive proof of a protrusion.

Myelography is useful to outline the protrusion and will show either (*a*) total block above the affected area or (*b*) bulge over the protrusion (Fig. 4). Thorotrast is a useful contrast agent in the dog since it is water-miscible and can outline several protrusions. It causes a lymphocytic meningitis, but does not appear to cause any clinical affection.

*Treatment*

Conservative treatment is mostly employed, and because of the high percentage of spon-

taneous recoveries assessment of the various methods is difficult. Disc fenestration is useful in the cervical protrusion cases.

*Prognosis*

Cervical cases: Usually good after operation, untreated cases show persistent pain with periods of normality. Paraplegics: Prognosis depends mainly on the time interval between the onset of the condition and the first sign of recovery. Seven days or less—good; four weeks or more—very poor.

Breed incidence: dachshunds are especially prone.

Hansen (1951) classified dachshunds, pekinese and French bulldogs as "chondrodystrophoid" and claimed that there was a relationship between the abnormal endochondral ossification in these breeds and the early disc degeneration which they exhibit. Spaniels are also commonly affected.

REFERENCES

DEXLER, H. (1896) *Öst. Z. Veterinark*, **7**, 1.
HANSEN, H. J. (1951) *Acta orthopæd. scand.*, **20**, 280.
OLSSON, S. E. (1951) *Acta orthopæd. scand.*, **20**, 349.
——, and HANSEN, H. J. (1952) *J. Amer. vet. med. Ass.*, **121**, 361.

**Dr. R. N. Smith** (Bristol):

*Anatomical Factors Influencing Disc Protrusion in Dog and Man*

It is now known that a number of locomotory disturbances can be traced to pathological conditions of the intervertebral disc not only in man but also in dogs, cats and even cattle. It is believed that the anatomy of the region influences the course of the disease and this paper will deal first with those anatomical features which may have a bearing on protrusion of a disc and then with what is known of the factors influencing the distribution of lesions and the differing syndromes in man and dog. Dr. A. S. King is associated with all that is presented in this paper.

The actual substance of the normal intervertebral disc is the same in man and the dog. In the relatively young animal a distinct annulus fibrosus surrounds the approximately central nucleus pulposus. The annulus has a narrow zone of collagen fibres and a deeper zone of fibrocartilage. The fibres of the annulus are continuations of the Sharpey's fibres of the vertebræ, originating from one centrum and pursuing an oblique course before inserting in the adjacent one. They are arranged in lamellæ and adjacent lamellæ have the direction of the fibres arranged at an angle to one another. In a cross-section of the disc the oblique fibres will be transected at different angles and the lamellæ will be seen not to form complete rings but to encircle about half the nucleus, when the ends may taper off or they may split and enclose the ends of other layers. Between the annulus and the nucleus is a narrow transitional zone which can only be seen satisfactorily in the young separating two structurally different tissues. However, as the nucleus ages and merges with the perinuclear tissue the transitional zone becomes much less apparent.

In the young the nucleus pulposus is a gelatinous mucoid mass infiltrated by a few collagenous fibres. It is believed that by virtue of its semi-fluid nature it can alter in shape during movement of its embracing vertebræ and so distribute the compression forces over the vertebral end surfaces. A direct end-to-end force will cause a flattening of the nucleus and this in its turn will be accommodated by outward expansion of the annulus. However, the nucleus soon loses both its mucoid appearance and its plasticity. Heavy fibres appear, dehydration sets in and a whiter firmer nucleus manifests the fibroid phase. In man the changes continue and fibro-cartilage replaces the originally plastic jelly.

The position of the nucleus pulposus relative to the disc changes during life. Early on it is fairly centrally placed but as growth of the vertebral column takes place on the side remote from the vertebral canal the nucleus will appear to migrate towards the spinal cord.

The shape of the disc is controlled by the conformation of the end surfaces of adjacent vertebræ. The human vertebra has a flat end surface covered by a very thin cartilage plate and surrounded by a raised rim. That of the dog is slightly convex with a dorsally eccentric concave area lined by cartilage. No doubt man achieves greater stability for his upright posture with the rings of contact of the vertebral bodies being peripheral, than he would if they were relatively central as in the dog. The nutrition of the disc is thought to be by diffusion from adjacent vertebræ as very few blood vessels are seen and these are usually peripheral.

It is not improbable that all the factors mentioned so far have some bearing on protrusion of the disc. By virtue of its position and morphology it is prone to degeneration and trauma. The disc of man begins to degenerate about the third to fourth decade, of most dogs at 6–7 years, and of certain breeds—the chondrodystrophoid group—at about 6 months. These are the times that one usually finds symptoms beginning in these different animals; the hardened nucleus can no longer distort to adapt to vertebral movement and instead will tend to be pushed against the annulus. This has lost its resilience and, instead of accommodating to the push, it breaks and fissures. The direction of the nucleus-pulposus-bullet must be

helped by its dorsal eccentricity and dorsal protrusions are commoner than those in any other direction. The part played by the shape of the disc and vertebra is uncertain.

It would appear at first sight that the distribution of protrusions along the vertebral column should parallel the distribution of degenerations. For the only two species in which comparisons are available (dog—Hansen, 1952; cat—King and Smith, 1958) the distributions are not very similar. There appears to be little detailed information on the distribution of protrusions in man. Haley and Perry (1950) give details for the cervical region (Fig. 1A) and Horwitz (1939) for the lumbar (Fig. 1B). In addition, Haley and Perry found very few

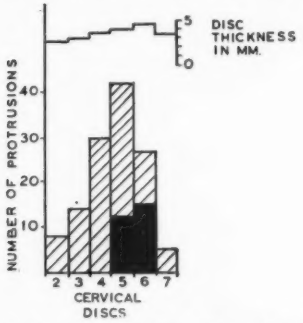



FIG. 1A.—Distribution of cervical protrusions found in a survey of 99 human cadavers by Haley and Perry (1950). The black columns represent protrusions over 4 mm. in height.

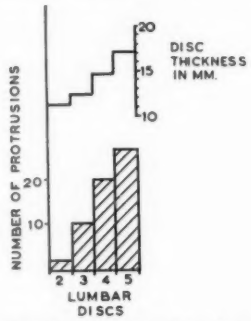



FIG. 1B.—Distribution of lumbar protrusions found in a survey of 75 human cadavers by Horwitz (1939). In both histograms the data for disc thickness are taken from Grant (1952).

protrusions from the thoracic discs. In the cervical region it will be seen that although there is not a strict correlation between the total number of protrusions and the thickness of the disc, the larger protrusions coincide with the thicker discs. There is still too much controversy over the sites and degrees of normal mobility to be able to decide the effect this factor has on the distribution of protrusions in man. In addition, it is not improbable that the mobility of a region will alter when it becomes degenerate.

There are two published surveys of protrusions in dogs (Hansen, 1952; Hoerlein, 1953), which when added together give the histogram Fig. 2. There appears to be some attraction

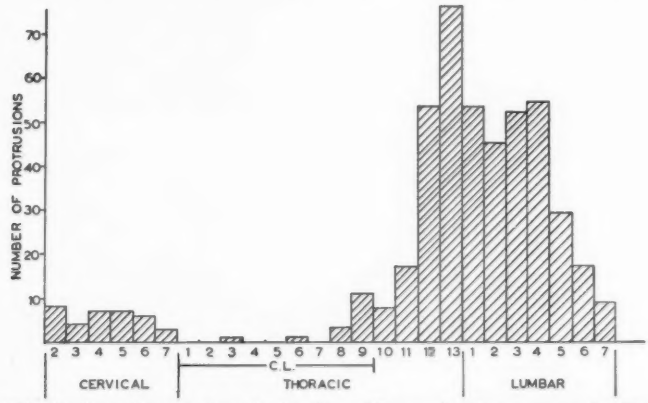



FIG. 2.—Distribution of protrusions in the dog. The results from surveys by Hansen (1952) and Hoerlein (1953) have been added together. C.L. is the region in which the conjugal ligaments are usually found.

for protrusions in the late thoracic and early lumbar regions, but until we know more of the qualities inherent in the canine vertebral column we are unable to explain the regional distribution. There is not a marked difference in the thickness of discs although those in the thoracic region show a tendency to be narrow. Regarding the effect of mobility, Stiper (1946) considers the most important centre to be in the region of the 10th thoracic vertebra.

We can, however, comment on the role the conjugal ligaments may play. These structures, which are not found as such in man, connect the heads of each pair of ribs from numbers 2 to 10 by running between the disc and the dorsal longitudinal ligament. Certainly in the dog protrusions do not often occur in the region of these ligaments except in the case of the last of the series and to a certain extent the penultimate. It may be argued that the last ligament is small and not so effective as the others, but King (1956) has shown that the first is of similar dimensions to the last yet protrusions have not often been described at the disc it covers. It is said that man has very few thoracic protrusions yet there is no conjugal ligament in that species. So, although the ligament may have a restraining action on protrusions we are inclined to think that most of the thoracic region differs in some way from the remainder of the column regarding the conditions for the protrusion of the disc.

Although pain sensations can arise from damage to structures intimately associated with the discs, damage to the central nervous system produces the most impressive symptoms. The site of the lesion is of paramount importance, but one should also bear in mind the suggestion by Olsson (1951) that it is not the size of the protrusion as much as the force with which it is projected that determines the symptoms. In man the end of the spinal cord is at the beginning of the lumbar region and only nerves fill the remainder of the relatively wide vertebral canal. Remembering that it is in the last few lumbar discs that protrusions are commonest in this region it will be seen that most of the effects will be grouped in the area of distribution of one or a very few nerves. But in the dog the cord finishes at the end of the lumbar region and so this species will suffer in rather a general manner wherever the protrusion occurs and, as is well known, the most severe of these cases result in paraplegia.

REFERENCES

GRANT, J. C. B. (1952) A Method of Anatomy. 5th ed. London.
HALEY, J. C., and PERRY, J. H. (1950) *Amer. J. Surg.*, **80**, 394.
HANSEN, H. J. (1952) *Acta orthopæd. scand.*, suppl. 11.
HOERLEIN, B. F. (1953) *Amer. J. vet. Res.*, **14**, 260.
HORWITZ, T. (1939) *Surgery*, **6**, 410.
KING, A. S. (1956) *Vet. Rec.*, **68**, 939.
——, and SMITH, R. N. (1958) *Nature, Lond.*, **181**, 568.
OLSSON, S. E. (1951) *Acta orthopæd. scand.*, suppl. 8.
SLIJPER, E. J. (1946) *Verh. Akad. Wet. Amst.*, Afd. Natuurkunde, Tweede sectie, Deel XLII, **5**, 1.

**Mr. Arthur Naylor** (Bradford):

*Changes in the Human Intervertebral Disc with Age*

The histological structure of the intervertebral disc and the changes in this with ageing have been described by Ross Smith (1931), Coventry *et al.* (1945) and Beadle (1931), but a more detailed investigation into the ultra-structure and constitution of the intervertebral disc was thought to be desirable if changes with age and their bearing upon function could be elucidated. Our investigations, conducted at the Bradford College of Advanced Technology with Drs. F. Happey and D. L. Smare of the Textile Studies and Physics Departments of that Institute, were pursued initially along two courses: (1) X-ray crystallographic studies of the disc structure at various ages and (2) Pressure measurements developed in the disc by fluid absorption. These led to our present investigations into the nature of the polysaccharides within the intervertebral disc, aiming later to estimate changes in protein and polysaccharide distribution and content with age.

*X-ray Diffraction Studies*

Our earliest investigations (Happey *et al.*, 1953; Naylor *et al.*, 1954) were made using fresh human intervertebral discs from subjects aged 3 weeks to 79 years, sections being partially dried in the air during examination. From the X-ray diagrams so obtained it was deduced that:

(*a*) The gels of the nucleus pulposus are made up of a dispersion of collagen molecules separated by a distance greater than the normal 11·8 Å found in fibrous tissues.

(*b*) With advancing age, the collagen becomes more and more orientated and it is evident that a degenerative process is at play until a stage of crystallization and fibrillation of collagen is reached in the discs of very old subjects as the nucleus loses its gel structure.

(*c*) In the annulus, a uniaxial dispersion of the crystallites of the collagen is seen before the age of 35, but specimens from older subjects show an increasing biaxial character. Beyond the age of 48, a preferred orientation appears to develop in the biaxial system, suggesting a tendency to reversion to the uniaxial orientation.

Our subsequent investigations show that some modification of these deductions is necessary.

Photographs taken with the X-ray beam parallel to the spinal axis and perpendicular to the radial direction of the disc show less dispersion than with the radial beam and suggest that fibrils are laid down in concentric cylinders around the radius in the plane of the cylinder. Using frozen sections 0·25 to 0·5 mm. thick to minimize air drying of the specimens, investigations were made using X-rays, infra-red spectroscopy and polarizing microscopy. Considerable diffuse scatter was produced in the X-ray diagrams of the very young specimens,

suggesting a swollen gel structure with its constituent collagen molecules in a randomly orientated condition. Increased resolution was seen in both annulus and nucleus with advancing age, but orientation was not apparent until the age of 35–38 years. Older specimens showed some encroachment of the nucleus by the annulus, being apparent in middle age and increasing with advancing years. Thus it would appear that the effect of ageing on the nucleus is a transformation from the dispersed gel structure to a fibrous desiccated collagenous mass (Figs. 1, 2, 3).

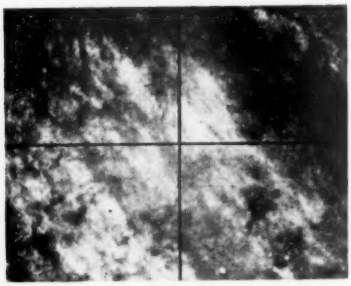


FIG. 1.

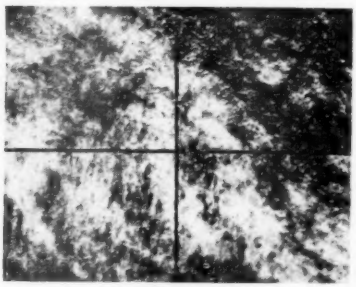


FIG. 2.

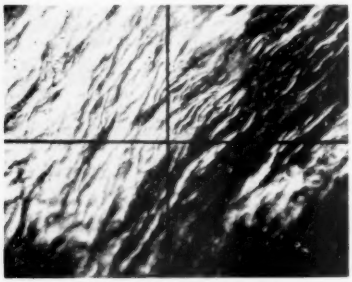


FIG. 3.

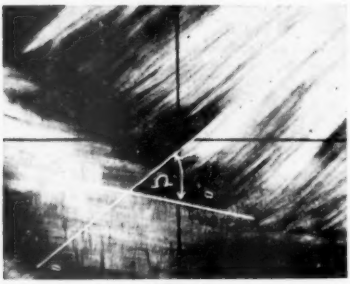


FIG. 4.

FIGS. 1, 2 and 3.—Polarizing micrograph of specimens of nucleus pulposus aged one and a half years, eight years and thirty-eight years respectively showing increased resolution.

FIG. 4.—Polarizing micrograph of annulus fibrosus from subject aged 63 showing interstriation angle.

Infra-red spectroscopy of specimens from subjects aged 65–70 and 78 all showed a possible β-protein structure superimposed on the typical collagen X-ray diagram, the spectra obtained suggesting the presence of a second non-collagenous protein in the nuclei of aged subjects.

Comparison of the X-ray diagrams obtained from the frozen un-dried specimens with those obtained by air drying for half an hour showed that the disorientated appearance in sections from the younger age group was an artefact produced by the drying. All age groups over 21 years gave a biaxial X-ray diagram and this was confirmed by examination with the polarizing microscope. Further, the ageing process of increased orientation beyond this age is seen only in the nucleus.

Using frozen sections 10$\mu$ in thickness, it was possible to obtain single sheets of collagen from the annulus. These sheets have a uniaxial arrangement when examined by the polarizing microscope and gave a highly orientated X-ray diagram. By this means it was shown that the biaxial diagram results from the annulus being formed by concentric uniaxial sheets laid against each other so that the fibres of each adjacent layer are set at an angle to those of the next layer—referred to as the interstriation angle (Fig. 4). This explanation of the biaxial diagram was confirmed by observing the angle between the collagen chains as measured from X-ray diagrams and comparing with the angle between the striæ of the uniaxial sheets as seen under the polarizing microscope. Good agreement between these angles was obtained.

Measurement of the thickness of single sheets from various parts of the annulus fibrosus showed large variations in thickness of the sheets and in parts of the individual sheets. During growth the thickness of the annulus probably increases by addition to the number of sheets laid down and certainly by increase in their thickness.

Specimens from varied parts of the annulus were examined to determine the presence or otherwise of any potential weak area which might be a factor in the development of a disc prolapse. Large variations in the interstriation angle were noted both in the actual circumference of the annulus and approaching the nucleus pulposus. In the specimens examined no obvious relationship between the interstriation angle, and position of the specimen in the annulus, or with age was apparent. Weiss (1953) and Lange (1929) have both shown that orientation of collagen fibrils is determined by the forces prevailing upon the tissues. Thus it is possible that the haphazard variation of the interstriation angle results from the stresses to which the annulus is subjected.

Hirsch and Nachemson (1954) when investigating the effects of compression in isolated discs reported observations of increase of the radius of the disc by 0·2 mm. when an additional 60 kg. was added to a disc already compressed by 40 kg. From our X-ray diagrams of stretched and unstretched annular sections, the variation in the interstriation angle with stretching can be estimated. From this it can be calculated that only 1° change would give the necessary change in radius, indicating that only a small change in the annular wall is necessary to accommodate the stresses to which the disc is subjected. Since the annulus shows a non-uniform arrangement of the sheets of collagen, the extension may not be uniform throughout the circumference. When the interstriation angle is small, greater shearing forces will be developed which may lead to weakening at that site. Attrition of the annulus is likely to develop from such repeated stresses. Alternatively, postulating only a certain angular change because of strong cohesion between the sheets of collagen, parts of the annular strands with large values for the interstriation angle will expand more than those with a low angle, implying that for a large value of the interstriation angle, a greater increase of circumference occurs and uniform pressure from within the nucleus is then apt to cause a localized attrition with subsequent bulging or herniation in such places. This is more prone to occur posteriorly where the annulus is thinner than elsewhere. Such factors are probably at play in the precipitation of a nuclear herniation by increase in intradisc tension produced by flexion of the spine.

The gel of the nucleus is deformable but incompressible and thus vertical forces are converted into radial forces which act on the annulus equally in all directions. The elastic properties of the annulus allow it to disperse these forces and normally this will prevent any small area of annulus receiving an unusually large pressure. We have seen how advancing age has a deleterious effect on both the gel properties of the nucleus and the elastic mechanism of the annulus.

To summarize, *in the nucleus* the increasing tendency to crystallization and precipitation of the collagen after the age of 30 inhibits the *uniform* transmission of stress to the annulus. A large stress may thus be placed on an isolated small portion of the annulus fibrosus, producing weakening and possible rupture of its fibres leading eventually to herniation of the nucleus.

*In the annulus* a process of reduced elasticity, or rigidity, is induced by the increased precipitation of the collagen and a reduction in the biaxial character of the fibrils.

The net result of these changes is an increased inability to withstand strain on the annulus, yet the loss of function by the nucleus as a result of diminution in gel structure throws much greater strain upon the annulus.

*Pressure Measurements*

The second and simultaneous phase of our work was concerned with the determination of intradisc pressure produced by fluid absorption and has been previously reported (Naylor and Smare, 1953; Bush *et al.*, 1956).

The decrease of the water content and fluid absorption capacity of the nucleus pulposus with age was demonstrated by Püschel (1930) and Göcke (1932). We repeated and confirmed these observations and noted that the addition of hyaluronidase to the immersion fluid increased the fluid absorption by 20%. Charnley (1952) also demonstrated this property of fluid absorption and showed that by this means a considerable pressure could be set up. We estimated pressures which were developed within intact discs when immersed in saline or water and demonstrated the development of pressures in the range of 8–300 cm. of mercury in young subjects whilst no pressures were developed in specimens from old subjects which showed disc degeneration (Naylor and Smare, 1953). These observations lead us to postulate a preliminary hypothesis, viz. that the possible sequence of changes leading to the development of the disc syndrome consists of a depolymerization of the polysaccharide of the collagen-polysaccharide complex in the nucleus pulposus due probably to some endocrine factor leading to increased power of water absorption, this in turn causing fluid absorption by the nucleus and resultant increase in the intradisc pressure.

In relation to this we have recently obtained promising results with the treatment of disc herniation by ACTH given by intravenous drip.

Extension of the preliminary investigations confirmed the preliminary results, the features noted in an analysis of the results being:

(1) A wide variation in pressures, not only with age, but with discs of the same subject.

(2) The relatively large percentage of discs recording high pressures in the 41–60 age group.

(3) Relatively low pressures in subjects over 60 years or more. Degeneration and cavitation were frequently present in those discs showing low or nil pressures.

This hydrophilic property of the nucleus pulposus may be explained by the osmotic pressure differences between the protein gel and the surrounding medium, this being duly influenced by the mucopolysaccharide content. Sylvén *et al.* (1951) showed that more hydrophilic groups of the mucopolysaccharide in the nucleus became attracted to the increased collagen molecules with advancing age and this may result in a decreased water-binding and pressure-developing capacity.

The precipitation of large orientated collagen fibres in the nucleus in elderly subjects, as shown by our X-ray crystallographic studies, will decrease the gel concentration in the nucleus. These two factors alone could account for the decrease in the ability of a disc nucleus in an elderly subject to develop a pressure within itself. Any reduction in the actual mucopolysaccharide content itself would assist this process.

The factors affecting the intradisc pressure are therefore:

(1) Amount of hydrophilic mucopolysaccharide. A relative decrease is apparent with increasing age.

(2) Concentration of the protein gel in the nucleus—this decreases with increasing age after the age of 40.

(3) Presence or absence of cavitation.

(4) Variations in elasticity of the annulus fibrosus. This varies with age, for each individual disc and in different parts of an individual annulus.

It is probable that the loss of gel structure in the nucleus may have an effect on the diffusion rate of fluid from the nucleus and may therefore affect the nutrition of the disc.

*The Mucopolysaccharides of the Intervertebral Disc*

More recently we have concentrated our investigations on an elucidation of the nature and concentration of the mucopolysaccharides in the intervertebral disc.

Use of metachromatic stains, e.g. toluidine blue, to estimate the relative amounts of mucopolysaccharide in the nucleus shows a decrease with advancing age of subject and this coincides with the degree of degeneration as determined histologically (Malmgren and Sylvén, 1952). This may indicate reduced concentration of mucopolysaccharide or may be due to the relative increased amount of collagen which occupies their polar groups.

A detailed investigation of the mucopolysaccharide components of the intervertebral disc has not yet been reported, but a review of the published work suggests that more than one type is present. Einbinder and Schubert (1950, 1951) and Malmgren and Sylvén (1952) have isolated fractions thought to be chondroitin sulphate, based on infra-red spectroscopic examination and estimation of electrophoretic mobility. Using chemical extraction, paper chromatography, paper electrophoresis and infra-red spectroscopy techniques, our more recent work (Hall *et al.*, 1957; Bernardi *et al.*, 1957) suggests that a keratosulphate is present. We have recently shown (1957) that both nucleus pulposus and annulus fibrosus contain chondroitin sulphate and keratosulphate, while small amounts of hyaluronic acid may be a minor constituent. We are at present endeavouring to elucidate this further and to estimate the relative amounts of each in the annulus and nucleus at various ages.

## REFERENCES


Beadle, A. O. (1931) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 161.

Bernardi, G., Happey, F., and Naylor, A. (1957) *Nature, Lond.*, **180,** 1341.

Bush, H. D., Horton, W. G., Smare, D. L., and Naylor, A. (1956) *Brit. med. J.*, ii, 81.

Charnley, J. (1952) *Lancet*, i, 124.

Coventry, M. B., Ghormley, R. K., and Kernohan, J. W. (1945) *J. Bone Jt. Surg.*, **27,** 105.

Einbinder, J., and Schubert, M. (1950) *J. biol. Chem.*, **185,** 725.

——, —— (1951) *J. biol. Chem.*, **191,** 591.

Göcke, C. (1932) *Arch. orthop. Unfallchir.*, **31,** 43.

Hall, D. A., Lloyd, P. F., Happey, F., Horton, W. G., and Naylor, A. (1957) *Nature, Lond.*, **179,** 1078.

Happey, F., Macrae, T., and Naylor, A. (1953) Symposium on Collagens. Faraday Society, London.

Hirsch, C., and Nachemson, A. (1954) *Acta orthopæd. scand.*, **23,** 254.

Lange, M. (1929) *Verh. dtsch. orthop. Ges.*, **23,** 230.

Malmgren, H., and Sylvén, B. (1952) *Biochem. biophys. Acta.*, **9,** 706.

Naylor, A., Happey, F., and Macrae, T. (1954) *Brit. med. J.*, ii, 570.

——, and Smare, D. L. (1953) *Brit. med. J.*, ii, 975.

Püschel, J. (1930) *Beitr. path. Anat.*, **84,** 123.

Smith, N. R. (1931) *Brit. J. Surg.*, **18,** 358.

Sylvén, B., Paulson, S., Hirsch, C., and Snellman, O. (1951) *J. Bone Jt. Surg.*, **33A,** 333.

Weiss, J. M. (1953) *J. exp. Med.*, **98,** 607.

## BOOK REVIEWS

**Fluid and Electrolytes in Practice.** By Harry Statland, M.D. 2nd ed. (Pp. xv+229; illustrated. 45s.) London: Pitman Medical Publishing Co. Ltd. 1957.

This book is one of the many published in recent years on electrolyte metabolism and the fact that a second edition has been called for in seven years indicates that it apparently fills a need.

The first part, in 10 chapters (138 pp.) discusses the general physiology and pathology of salt and water metabolism, and therapy in general terms: the rest of the book considers specific clinical conditions where electrolyte imbalance is of importance, including chapters on heart disease, kidney and renal disorders, diabetic acidosis and pædiatrics.

The description of changes through loss of water and/or salt is in general clear, but the various figures are not as clear as they might be, nor are they mutually consistent. In Figs. 6 and 7 variations in tonicity are shown by shading and figures, but height of fluid columns are the same whether hyper- or hypotonic, and alteration of intra/extra-cellular fluid ratio is shown by a shift of the vertical dividing line between compartments. In Fig. 8, loss of fluid is shown by a fall in the horizontal boundary of the plasma and interstitial compartments: and the beginner might well think that the cell fluid takes no part in the adjustment: it would probably be clearer if Fig. 13 showing the adjusted condition followed immediately, or was referred to in the text accompanying Fig. 8.

In Figs. 11 and 12, the important changes in the hæmatocrit are very difficult to appreciate in the scale on which they are drawn and are quite overshadowed by the curve showing the changes in eosinophil counts, which from the practical point of view is of minor significance.

**Recent Trends in Chronic Bronchitis.** Ed.: Neville C. Oswald, T.D., M.D.Cantab., F.R.C.P.Lond. (Pp. vii+200; illustrated. 30s.) London: Lloyd-Luke (Medical Books) Ltd. 1958.

Dr. Neville Oswald and his colleagues are to be congratulated on providing a valuable addition to the literature on this important subject. The bronchitis clinic at the Brompton Hospital has, under Dr. Oswald's general supervision, involved team work integrating clinical, bacteriological and pathological studies. An excellent chapter on "Air Pollution and Chronic Bronchitis" by Dr. Patrick Lawther deserves special mention and the original studies of Dr. Lynne Reid on "The Pathology of Chronic Bronchitis" and those of Dr. Robert May on "The Bacteriology of Chronic Bronchitis", are of great interest and importance. The contribution of Dr. Ronald Gibson on "The Heart in Chronic Bronchitis and Emphysema", that of Dr. George Sims on the radiology, and that of Dr. Horder on "Aspects of Bronchitis in General Practice", also deserve special mention.

**Hormonal Regulation of Energy Metabolism.** Ed.: Laurance W. Kinsell, M.D. (Pp. xiii + 242. 40s.) Springfield: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

This book is the verbatim account of a conference held in America, on carbohydrate, fat and protein metabolism in the energy processes of the body, and their control by hormones. The conference was attended by distinguished experts in various parts of the field. Two sessions were devoted to more general aspects, and one each to the actions of the anterior pituitary, pancreas, adrenal cortex and thyroid. Introductory papers were read by appropriate experts and these were followed by discussions usually longer than the introductory papers themselves. The known facts about each aspect of the subject were reviewed and much recent experimental work by the experts present and others was reported and discussed. The book is hard going, but does manage to present a remarkably full and up-to-date account of the present situation in the field.

It is a difficult subject, and this book is for the specialist, not the general reader. The biochemist and the clinician interested in endocrinology and metabolism will, however, find much in it which is interesting, instructive and stimulating.

**Chronic Bronchitis in Newcastle upon Tyne.** By A. G. Ogilvie, M.D.Dunelm, F.R.C.P.Lond., and D. J. Newell, M.A.Cantab. (Pp. vii + 115; illustrated. 15s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

Medico-social surveys conducted on a wide scale in selected localities have lately been introduced into epidemiological and clinical research. They have been applied in particular to respiratory disease and the value of this method of investigation is again emphasized in the present report on "Chronic Bronchitis in Newcastle".

The authors early on discuss the vexed question of definition. They regard the two essential

symptoms as cough and sputum and the guiding principle to be the persistence of these symptoms for three months or longer during the winter: only in this way could they be certain of including examples of the disease in an early stage. The sample consisted of every fortieth house on the voters' register of the City. The initial enquiry was conducted by a health visitor who interviewed every occupant of the house over the age of thirty years and this was followed by medical examination. In all, 3,866 persons were included in the sample of which 1,202 were examined in detail. The object was not so much to elucidate the clinical patterns of the disorder as to establish the diagnosis and incidence and to study any possible ætiological factors that might be involved.

Several interesting conclusions were drawn. At the end of the book following the bibliography some of the facts are recorded in series of appendices. The whole book proves an admirable study of the subject and is itself so condensed as to be difficult to summarize.

**Ideals in Medicine.** A Christian Approach to Medical Practice. Eds.: Vincent Edmunds, M.D., M.R.C.P., and C. Gordon Scorer, M.B.E., M.D., F.R.C.S. (Pp. xi + 192. 12s. 6d.) London: The Tynedale Press. 1958.

Since there have been so many changes in the doctor-patient relationship as a result of the National Health Service, it is not surprising that more should be written concerning the ethics of medical practice and this book is a useful addition to the literature of this subject. It consists of fourteen chapters in which eleven other contributors have assisted the editors.

The book represents the findings of a Study Group of the Christian Medical Fellowship and it is essentially a description of the Christian approach to medical practice. It differs slightly from two other contributions to this subject which have recently been published, namely Maurice Davidson's "Medical Ethics: a Guide to Students and Practitioners" and the issue of *The Practitioner* in July 1957 devoted specially to medical etiquette, though naturally all three have much in common.

This book should make a special appeal to the medical student or recently qualified doctor, because it gives such a good account of the possibilities for the expression of Christian ideals in many different fields of medical practice. For instance the third chapter by E. G. Housden eloquently describes the satisfaction a family doctor may get from his work, and the sixth and seventh chapters by A. P. Waterson on the control of life and on the Christian approach to the disabled, the incurable and the dying, are particularly well written and well documented. The two Editors are certainly very fortunate in the choice of their collaborators, all of whom have succeeded in discussing the modern problems of medical practice in an enlightened and often in an inspiring way.

**A Theory of Disease.** By Arthur Guirdham. (Pp. 204. 21s.) London: George Allen & Unwin Ltd. 1957.

The author of this book, in his introduction, states that if he were required to summarize in a sentence its fundamental theme he would say that it is his belief that health is a by-product of religious experience. He feels that repression of varying degree determines the onset of illness, and suggests that the neuroses follow relatively mild repressive forces, functional disorders more powerful ones, and organic disease the most profound.

His ideas are attractively presented as he has a felicitous pen, and a theory of disease is in itself a subject to stimulate thought.

Dr. Guirdham addresses himself to a wider audience than the medical profession, and it will be for his individual readers to decide for themselves whether they can accept his views. At any rate they should enjoy making up their minds.

**Histology.** By Arthur W. Ham, M.B., F.R.S.C. 3rd ed. (Pp. xv + 894; illustrated. 80s.) London: Pitman Medical Publishing Co. Ltd. 1957.

In his preface to the third edition the author claims that there has been a "major revolution" in histology since 1950, due to the introduction of electron microscopy. The book is in fact now based on 582 photographs and drawings, of which about 70 are electron micrographs. The remainder are mainly more classical low- and high-power photomicrographs, with 8 colour plates and diagrammatic drawings. The standard of photography is of the highest, and certain of the high-power photomicrographs are some of the best yet seen. Around all this the text is simple and straightforward. The book is divided into four parts: (I) The method of study, including details of the use of the phase contrast and interference microscopes, with an excellent description of the workings of the electron microscope; (II) Cytology, including blood cytology; (III) The four primary tissues individually described; and (IV) The integrated systems, so that the student is taken from the elementary and isolated cell up to the integrated study of, for example, the circulatory system.

# Section of Anæsthetics

President—B. L. S. MURTAGH, M.B., F.F.A.R.C.S.

[*March* 7, 1958]

## DISCUSSION ON THE EXTRACORPOREAL CIRCULATION

**Dr. H. C. Churchill-Davidson** [*Abridged*]:

### INTRODUCTION

THE search for the ideal method of producing a " dry field " in cardiac surgery has centred largely around hypothermia and the extracorporeal circulation. Owing to the increased irritability of the myocardium the original hopes and expectations from hypothermia have not been realized, since under present conditions few anæsthetists would feel justified in lowering the patient's body temperature below 30—29° C. This temperature, however, only permits—with any degree of safety—interruption of the circulation to the brain for between 5 to 8 minutes. Until the problem of the increased irritability of the myocardium at lower temperatures can be solved the limitations of this technique are evident. On the other hand, the extracorporeal circulations—though more difficult to carry out—offer almost unlimited time to the surgeon when all the technical difficulties have been overcome.

In this presentation the principal forms of extracorporeal circulation in common use are reviewed without bias.

*History.*—In the latter part of the nineteenth century there were many references in the literature to the use of bubble and disc oxygenators. The principle of the bubble oxygenator is both obvious and simple, but nevertheless many workers preferred to use paddles which dipped down into a trough of blood and carried a thin film of it upwards into an atmosphere of oxygen—i.e. disc oxygenator. The difficulties under which these early investigators worked can be appreciated only when one recalls that it was not until 1916 that the first anti-coagulant was discovered. At that time Jay Maclean—a second year medical student at Johns Hopkins University—was investigating the clotting powers of certain phosphatides when he accidentally discovered one that actually prevented coagulation of blood. Further studies revealed that this substance could be found in reasonable quantity in the dog's liver; in this way heparin became available for the first time.

In 1937, Gibbon in Philadelphia started work on an extracorporeal machine, and after experimenting with various types of oxygenator he finally settled for one that involved the use of fixed metal screens over which the blood flowed in a thin film. Essentially, it is this machine that has been so successfully adapted and applied by the Mayo Clinic in recent months. In 1953, Andreasen and Watson published the results of their investigation on the importance of even a limited blood flow to the brain. After three minutes of total arrest of the circulation all their dogs showed signs of irreparable cerebral damage. If, however, the vena azygos flow was allowed to continue—representing about one-tenth of the normal cardiac output—then a large proportion of their animals were able to withstand up to forty minutes of this modified circulatory arrest. The principle, therefore, that even a small cerebral blood flow was sufficient to prevent irreparable damage became established, and it was soon brilliantly exploited by Lillehei in his application of the cross-circulation techniques to man. In these cases the parent acted as donor for a child, supplying it with sufficient arterialized blood to prevent cerebral injury. Nevertheless, the possible dangers of embolism to the donor raised both ethical and psychological objections, and the donor was soon replaced by a simple machine—the Lillehei-De Wall bubble oxygenator.

*Machines.*—The various heart-lung machines consist essentially of two components—the pump and the oxygenator. The problem of circulating blood round a machine is relatively simple compared with that of oxygenating suitable quantities of blood.

There are three principal types of pump available: (1) *Finger* or *sigmamotor* pumps massage suitable tubing in a manner similar to a hand running up the keys of a piano. The flow is unidirectional and almost nonpulsatile. (2) *Roller* pumps are similar to those used for squeezing tubing of a blood transfusion apparatus. Like the finger pump, the flow is both unidirectional and almost non-pulsatile. (3) *Compression* pumps squeeze a whole length of tubing evenly. The result is that the flow is not unidirectional unless this type of pump is combined with a valve or cam system. Furthermore, the flow is pulsatile.

The requirements of the ideal pump have not yet been determined. Clearly, it must

produce the minimum degree of trauma to the blood and must also be capable of delivering a normal cardiac output (i.e. 5 litres per minute). The question as to whether the flow should be pulsatile or non-pulsatile is also unsettled.

Venous drainage is usually obtained by simple gravity drainage on the same basis as one empties a fish tank. Alternatively a low suction system can be used.

There are in use at the present time innumerable machines, but basically they are of four main types, depending principally on the method of oxygenation used.

(1) *Bubble oxygenator.*—The Lillehei-De Wall is the most outstanding example of this type of machine. Venous blood passes to the bottom of a tall bubbling chamber measuring approximately 36 in. by 2 in. (Fig. 1). Oxygen enters under pressure through a number of

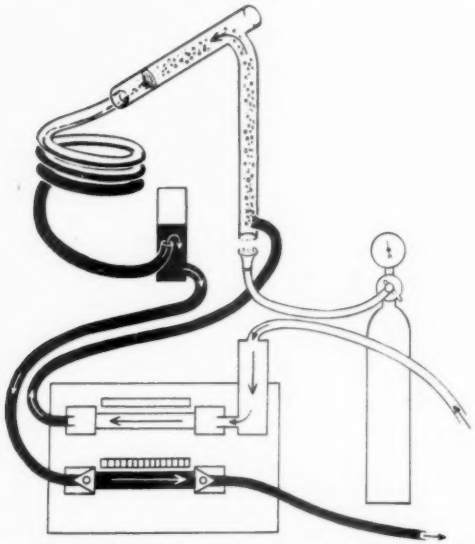


FIG. 1.—Diagram of Lillehei-De Wall oxygenator. Blood enters the venous reservoir on the left and is then pumped to the base of the vertical bubbling chamber (*see* text).

fine holes at the base of this column and thus carries the blood upwards as a mass of foaming bubbles. At the top of this chamber it falls over into a collecting tube and starts on its slow run down to the de-bubbling chamber. This latter vessel is a long length of polythene tubing arranged in a spiral fashion so that the oxygenated blood now gradually winds its way downwards to the arterial reservoir. During its passage it is hoped that any small bubbles that are still present will be induced to come to the surface. The critics of this type of machine claim that small bubbles are actually carried over to the patient. Essentially, it is a low flow machine, in that it does not attempt to supply the patient with as much as his normal cardiac output. Nevertheless, more recent developments suggest that the margin between high and low flow machines is gradually diminishing as the output of the latter increases.

(2) *Disc oxygenator.*—The Melrose machine is a good example of this type (Fig. 2). The oxygenator consists of a series of plastic plates, each hollowed out with a differently set eccentric hole, so that they act as innumerable traps for the blood as it passes down the oxygenator, which is arranged at an inclined level. As the whole oxygenator rotates around a central axis the blood is distributed evenly over the walls of each trap before spilling over into the neighbouring compartment. The arterial reservoir forms at the lower end of the oxygenator and from here the blood is sucked up and passed to the patient by a compression pump.

(3) *Screen oxygenator.*—The Gibbon machine is the classical example of this type of oxygenator. Here a series of metal screens is arranged vertically in a plastic casing. At the top of each screen the blood runs along very fine channels so that it is distributed evenly across the whole length of the screen. As it flows downwards in a thin film it is exposed to an atmosphere of oxygen, finally congregating in the arterial reservoir at the base of the oxygenator. In the Mayo modification of the Gibbon machine (Patrick *et al.*, 1957) the

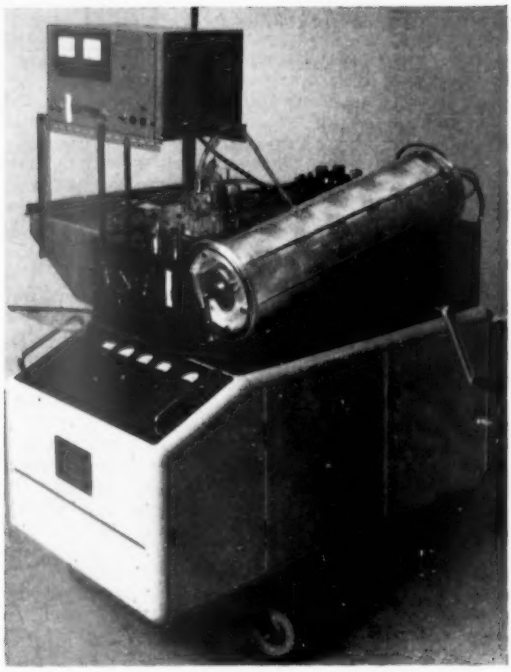


FIG. 2.—Melrose pump-oxygenator, with an electro-magnetic flowmeter mounted above it.

arterial line leaving this reservoir splits into two channels. One carries arterial blood direct to the patient whereas the other passes back through an electrically controlled clamp so that it rejoins the venous line on its way to the top of the oxygenator. As the flow through this recirculation channel is controlled by changes in level in the venous reservoir, it is possible automatically to obtain rapid adjustments between venous and arterial flow. For example, a sudden increase in the level of the venous reservoir results in a partial obstruction of the recirculating channel which makes more arterial blood pass to the patient.

(4) *Membrane oxygenator.*—The physiological principles underlying this method of oxygenation make it theoretically superior to the other methods, yet the technical difficulties are much greater. A thin plastic membrane is placed between the blood on one side and the gases on the other so that the blood never comes directly in contact with the atmosphere. Essentially this membrane apes the part played by the alveolar epithelium in the lung. The efficiency of this type of oxygenator depends on the speed at which the various gases will traverse its walls, and therefore on the property of diffusibility of the plastic membrane. This type of oxygenator removes many of the dangers of air embolism created by the other methods mentioned above. It has great possibilities for development in the future.

## REFERENCES

ANDREASEN, A. T., and WATSON, F. (1953) *Ann. Roy. Coll. Surg. Engl.*, **12**, 261.
PATRICK, R. T., THEYE, R. A., and MOFFITT, E. A. (1957) *Anesthesiology*, **18**, 673.

**Dr. Cyril F. Scurr:**

*Cardio-pulmonary By-pass: Physiological Considerations*

The aim and object of this procedure is to permit the repair under direct vision of intra-cardiac defects on the open and preferably dry heart. For example, closure of a ventricular septal defect with an Ivalon patch might require a 20-minute period—in some centres procedures lasting up to one hour appear to be routinely successful. Throughout this period of by-pass of the patient's heart and lungs, apparatus is required to sustain the functions of circulation and respiration. This circulation must ensure adequate perfusion with arterialized blood of the vital organs, especially the brain.

*The By-pass*

I should like first to consider how the by-pass is accomplished (Drew *et al.*, 1957). After induction of anæsthesia thoracotomy is performed; both venæ cavæ and also the left subclavian artery are mobilized and the azygos vein is ligated. The subject is heparinized and then two plastic tubing cannulæ are introduced via the right atrium, one into the superior and the other into the inferior vena cava; the arterial cannula is inserted into the recipient artery. All three cannulæ are then connected to their respective lines to and from the apparatus. At the moment of by-pass tapes which encircle the cavæ are tightened so that the caval wall is closely applied to the cannulæ: all the venous flow is therefore directed through the cannulæ to the machine. In cases where elective cardiac arrest is induced a clamp is also placed across the proximal aorta. When this is not done the coronary arteries are perfused and the resulting venous return from the coronary sinus is added to that from the bronchial vessels; this blood obscures the operative field and is also lost from the circuit—it must be accurately replaced or returned to the machine.

*The Flow Rate*

Technical difficulties and some dangers may arise when flows approximating to the normal cardiac output are returned via a subclavian cannula, as it is very narrow relative to the aorta which is normally adapted to carry such a flow. Very high pressures are obviously required, especially if the cannula is unduly small; this leads to increased hæmolysis and there may be jet formation with damage to the vessels.

The early work of Andreasen (Andreasen and Watson, 1952, 1953*a*, 1953*b*) showed that dogs could survive clamping of the cavæ for a period of 30 minutes, the cardiac output being limited to the small return flow through the vena azygos. These findings were confirmed by others (Cohen and Lillehei, 1954) and in many centres it has since been shown that a flow rate of 40 ml. per kilogram body-weight per minute is sufficient to ensure survival. This is a *low flow*, because it is less than half the normal cardiac output. We have regarded this figure as a minimum and have always used higher flows in our human cases. In practice the arterial pump is set to deliver a flow determined by the body-weight (or surface area), the reservoir being kept in balance by regulating the venous pump. An alternative is to give an arterial perfusion rate equal to the maximum venous return obtainable by the machine. The amount of venous return available is, in any case, the factor ultimately limiting output.

It has recently been shown (Paneth *et al.*, 1957) that when gravity siphon venous drainage is used the total venous return is equal to the output of the arterial pump over the whole range of perfusion rates studied. Thus, with this system, accurate balance is simplified.

Working with this type of apparatus Paneth *et al.* (1957) reported that at a perfusion rate of 1·2 litres per sq. metre per minute, equivalent to 60–70 ml. per kilogram per minute in dogs, the oxygen consumption levelled off, indicating that basic tissue requirements for oxygen were being supplied. They also noted that at this perfusion rate arterial pressures approached physiological levels. Evidence was obtained to show that with this flow the degree of metabolic acidosis was similar to that observed in animals merely subjected to 60 minutes of anæsthesia with the chest open. The development of metabolic acidosis was inversely related to oxygen consumption and in direct proportion to the duration of perfusion.

It seems, therefore, that 1·2 litres per sq. metre per minute represents an optimum, avoiding the technical difficulties of higher flows and yet taking care of internal or cellular respiration requirements. In cyanotic patients a higher rate has been recommended to make up for losses via the bronchial collateral circulation.

Apart from the amount of the flow, distribution is of vital importance, especially with low perfusion rates.

The cardinal danger of inadequate flow or improper distribution is cerebral ischæmia and, as I hope to show later, adequate warning of this danger is given by the EEG, which we think provides a valuable guide to cerebral blood flow. Paneth *et al.* (1957) quote data to show that the oxygen needs of the heart and brain are met by a total flow rate less than half that required by the tissues draining into the inferior caval system.

Inadequate perfusion of the rest of the body, if minor in degree, allows, as already seen, the development of metabolic acidosis: in severe degrees diffuse anoxia leads to damage to the cell membranes with loss of potassium ions from the cells and hyperkalæmia. A falling sodium level in the blood indicates anoxic failure of the sodium pump mechanism.

*External Respiration*

We have seen that internal respiration is dependent on adequate perfusion: external respiration—the gross provision of oxygen and elimination of carbon dioxide—must now be considered. The oxygenator will deliver blood with 95% or better oxygen saturation. In our cases the returning mixed venous blood has been 50–60% saturated. This would

seem to provide evidence of adequate oxygen utilization and supply, for much higher degrees of venous unsaturation would be expected if the supply were inadequate.

With regard to carbon dioxide balance: in some centres 5% $CO_2$ in oxygen has been used in the oxygenator, the blood coming into equilibrium with an atmosphere similar to alveolar air. In our own series 100% oxygen has been used, the $CO_2$ being allowed to escape freely from the oxygenator. Despite this we have no evidence of $CO_2$ lack; unfortunately $pCO_2$ estimations were not available, but the pH readings have always been slightly on the acid side of normal.

The blood—albeit stored for a minimal time—with which the machine is primed is always highly acid, the pH being about 6·8. Much of this is due to fixed acid, as passage through the oxygenator raises it to only 7·0–7·1. As the volume in the machine may exceed the blood volume of the recipient, the early production of acidosis in the subject is not surprising. A sign of this may be the onset of spontaneous respiration often observed at the start of perfusion on a subject hitherto apnœic. A further danger in the stored blood lies in the fact that it may have a very high potassium level which could lead to adverse cardiac effects should such blood perfuse the coronary system; use is indeed made of potassium to produce elective cardiac arrest.

The methods of monitoring the various physiological variables during the procedure are listed in Table I; some of the information helps in the control of the perfusion. The EEG and ECG are recorded on two channels of an Ediswan 4 pen recorder.

TABLE I.—OBSERVATIONS DURING CARDIO-PULMONARY BY-PASS

1. Electroencephalogram.
2. Electrocardiogram.
3. Central arterial pressure.
4. Central venous pressure.
5. Body temperature.
6. Oxygen saturations—venous and arterial.
7. pH values—venous and arterial.
8. Biochemical estimations—Na, K, $HCO_3$.

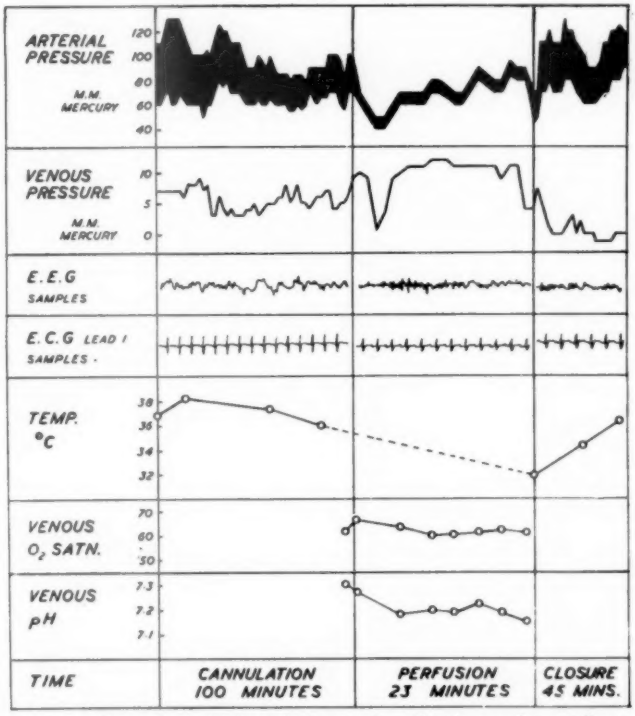



FIG. 1.—Recordings obtained during total cardiac by-pass in an infant.

The arterial and venous pressures are recorded on the other two channels from capacitance manometers connected to cardiac catheters placed in the aorta and inferior vena cava

respectively via the femoral vessels. Oxygen saturation and pH values are determined every three minutes during perfusion, samples being obtained from the venous or arterial line as desired.

Fig. 1 summarizes some of the observations during an operation on an infant—the period on by-pass was 23 minutes; the perfusion rate was 45 ml./kg./minute. It is seen that the arterial pressure during the by-pass period was lower than previously, but, nevertheless, it was sustained at a reasonable figure. The venous pressure was fairly high during the by-pass procedure. The EEG shows a satisfactory degree of activity, indicating adequate cerebral perfusion. From the ECG it is seen that the heart continued to beat spontaneously throughout. It is noteworthy that, despite a warming mattress and a 37° C. waterbath round the reservoir, the temperature fell to 32° C. during the perfusion—a similar fall was observed in all cases.

The venous oxygen saturation was steady at around 60% during the perfusion, which implies an adequate supply of oxygen.

Early in the perfusion the venous pH fell, due presumably to the acid reaction of the blood from the machine, but the readings remained fairly stable at about 7·2, i.e. there was no evidence of *progressive* acidosis.

Fig. 2 is a record obtained during by-pass in a dog, showing the arterial pressure running at about 60 mm.Hg and the absence of pulse pressure during the perfusion. The EEG is seen to be active and satisfactory; but the ECG, though regular, is abnormal.

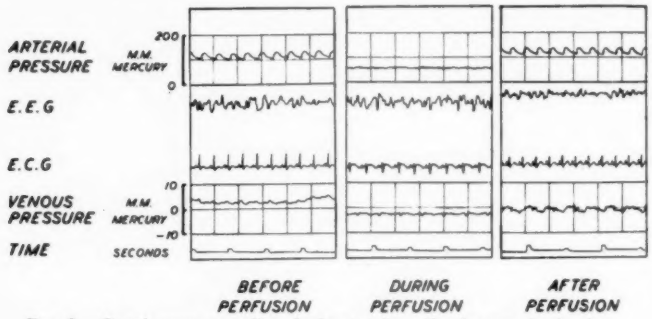



FIG. 2.—Continuous recording during total cardiac by-pass in the dog.

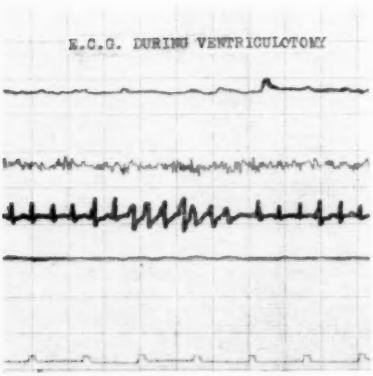



FIG. 3.




FIG. 4.

As seen from the aortic pressure at the top, Fig. 3 was a record obtained during perfusion. At the moment of ventriculotomy a characteristic shower of ventricular extrasystoles is seen.

More recently we have employed elective cardiac arrest with potassium, as described by Melrose (Melrose *et al.*, 1955). The technique was as follows: 2 ml. of 25% potassium citrate was mixed with 18 ml. of blood in a syringe, and enough of this mixture to produce cardiac arrest was injected between a clamp placed on the ascending aorta and the coronary ostia. The onset of arrest in a dog is seen in the upper two lines of Fig. 4. After the cardiotomy period the aortic clamp was removed and, with the restoration of coronary perfusion, the heart beat recommenced after a period, as shown in the third trace. In some instances the delay was as long as 10 minutes. Electrolyte changes following potassium-induced arrest are of interest. The plasma K level in the vena cava was only 4·8 mEq./l. five minutes after removal of the aortic clamp, although the concentration in the first blood sample from the coronary sinus following arrest was 15·2 mEq./l. The relatively small amount of potassium injected is itself insufficient to cause any significant change in plasma K when distributed throughout the circulation.

A further difficulty experienced in the dog was the liability for bleeding to occur from the site of injection into the aorta. In two experiments this was the cause of death, as the bleeding persisted from the puncture during the post-operative period—the wall of the dog aorta is notably thin and it is safer to inject via the left ventricle. This experience with potassium-induced arrest in dogs contrasts with our findings in human cases: in these the heart stopped almost immediately after the potassium injection (Fig. 5) and normal rhythm was rapidly re-established afterwards, no complications arising from bleeding at the injection site.

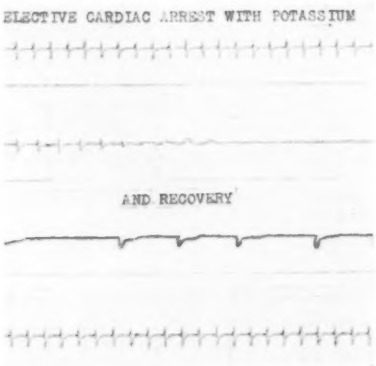



FIG. 5.

*Central Nervous System Damage and Electroencephalography*

In the experiments which had a fatal outcome the most frequent cause of death, apart from hæmorrhage, has seemed to be damage to the central nervous system. This can arise in a variety of ways: for example, embolization, acidosis, or inadequate perfusion with resulting anoxic damage.

With regard to embolization (Giannelli *et al.*, 1957), it has been shown that embolic brain damage can result from gas bubbles, fibrin particles or excess antifoam substance. The use of *excessive oxygen* flows in the bubble oxygenator is followed by a high incidence of severe brain damage.

In our experience and that of others (Paneth *et al.*, 1957; Theye *et al.*, 1957) the EEG has been a sensitive and valuable index of cerebral well-being. We have so far obtained no evidence of cerebral embolization in our own cases, but I must draw attention to the experimental work of Karlson (1957), who was unable to demonstrate significant EEG changes in dogs subjected to deliberate gradual carotid air embolization, ultimately fatal in degree.

It seems probable that the EEG is not an accurate indicator of brain damage resulting from cerebral gas embolism.

*Acidosis.*—Clowes (1957*a*) states that metabolic acidosis leads to delayed recovery or, if more intense, to severe EEG depression and failure to survive. He also reports (Clowes, 1957*b*) that, if a dog is given carbon dioxide and the brain wave is absent for over fifteen minutes, one can predict that the dog will not recover.

The EEG pattern characteristic of light anæsthesia is of 20–24 cycles per second frequency and of 30–40 microvolts in amplitude. With inadequate cerebral perfusion an early abnormality was an increase in amplitude up to 300 microvolts with a frequency of 1–2 per second or less (Drew *et al.*, 1957). If not remedied, the EEG progressed to a flat and inactive pattern, and it has recently been demonstrated that six distinct stages can be recognized in this process (Hudson, 1958). Other factors may also produce flattening of the EEG, but one can easily recognize the gradual onset of typical EEG signs of increased depth of anæsthesia.

Hypoglycæmia and hypothermia have a similar effect; although hypothermia of mild degree occurred in these experiments, it did not approach the level of 20–23° C. necessary for the *first type* of EEG change or the 15° C. at which flattening might be expected (Libet *et al.*, 1940).

No data are available to correlate the EEG changes quantitatively with cerebral blood flow, nor to infer distribution of cerebral flow from the total systemic flow. But in our experience, if flattening of the EEG due to *inadequate perfusion* is allowed to persist for more than a few minutes at normal temperature, it is likely that the animal will fail to survive.

This record (Fig. 6) demonstrates deterioration of the EEG in a dog during perfusion via the brachial artery (7 kilos—perfusion rate 40 ml./kg./min.). This dog failed to survive.

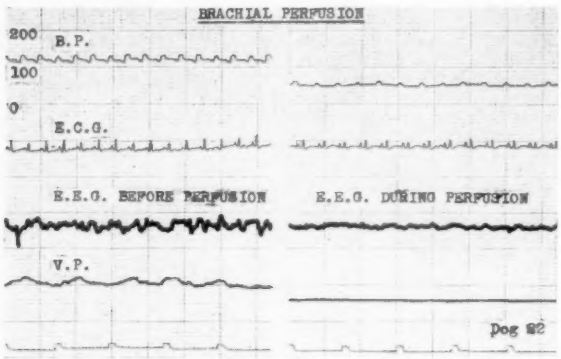



FIG. 6.

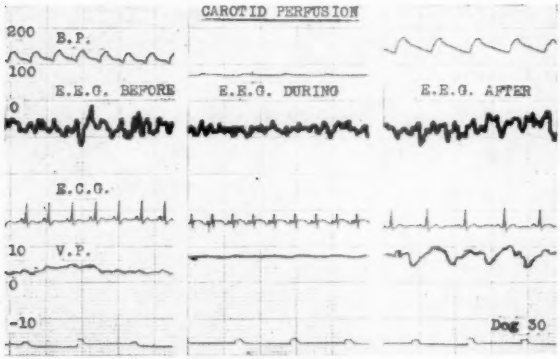



FIG. 7.

In the next record (Fig. 7), with systemic perfusion at the same rate but via the carotid artery, it is seen that EEG activity is satisfactorily maintained throughout. This dog survived.

In the *human*, perfusion via the left subclavian artery has been carried out in a number of cases without any evidence of deterioration in the EEG or clinical evidence of brain damage post-operatively.

The top line of this record in Fig. 8 shows the EEG of a 9-months-old child (6½ kg.), immediately after the induction of anæsthesia. Increasing the depth with ether produces the typical changes seen in the second line. Half-way along the third line an abrupt change is seen: high voltage and low frequency; at this point the bilateral thoracotomy had been completed and the chest spreader opened out to an extreme degree. The EEG rapidly progressed to a flat pattern, indicating the onset of cerebral anoxia (3.53 p.m.). The chest retractor was promptly released and the stages of recovery are clearly seen in the lower two

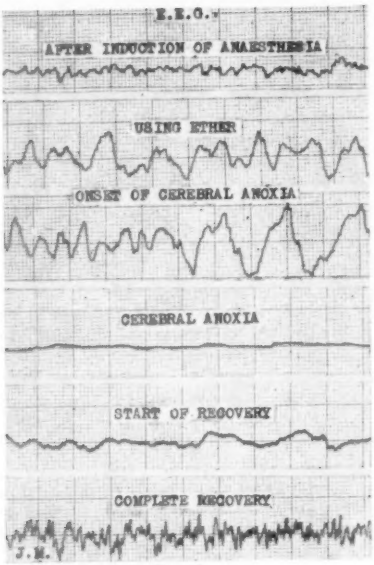



FIG. 8.

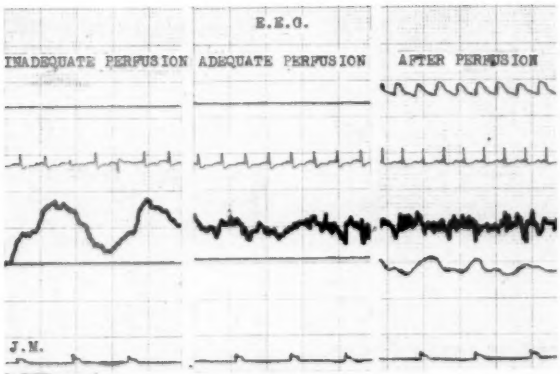



FIG. 9.

lines (last line 4.03 p.m.). The excessive spread of the retractor had apparently caused superior caval obstruction, so interfering with cerebral blood flow.

A similar effect resulting from s.v.c. obstruction during cannulation has also been observed (Theye *et al.*, 1957).

At a later stage—during the by-pass period—the EEG of this same baby again showed signs of cerebral anoxia, as seen in the first portion of Fig. 9. This was due to a transitory fall in pump output. When this was corrected and the perfusion rate speeded up, the EEG is seen to return to normal.

UNIVERSITY OF MICHIGAN LIBRARIES

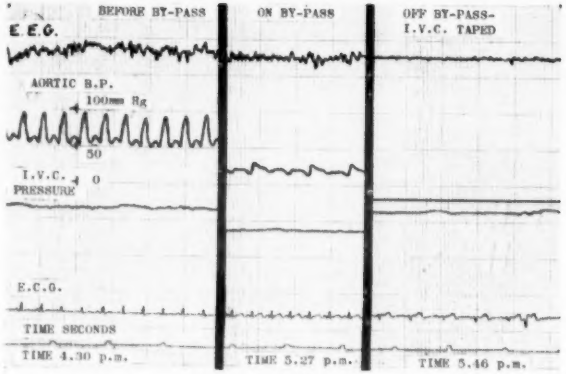



FIG. 10.

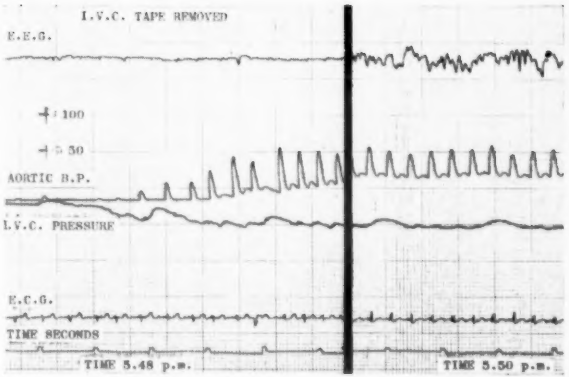



FIG. 11.

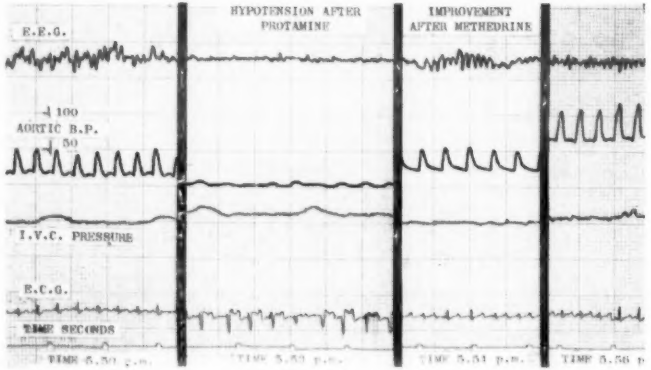



FIG. 12.

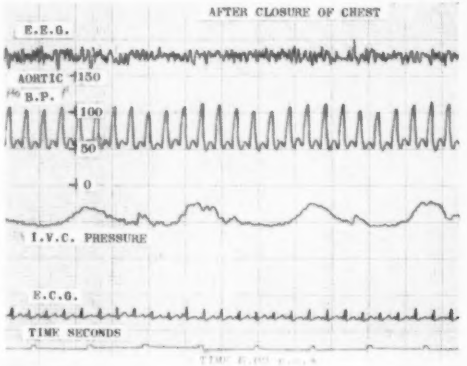



FIG. 13.

The opinion is sometimes expressed that the EEG only indicates that the animal is dead at about the time that it is already obvious from all the other signs. In our belief this opinion results from *inadequate* EEG technique. We believe that the activity of the EEG is the best index of satisfactory cerebral blood flow and cortical viability. Timely warning is provided so that measures can be taken to ensure survival. Two examples of this have already been seen. In further support of this view I present these last records obtained during a single experiment on a dog.

Fig. 10 shows the record before the by-pass: during the period on the machine nearly one hour later it is seen that the EEG is well maintained.

After the by-pass the inferior caval tape was inadvertently left in position and inadequate venous return, gravely impairing cardiac output, led to profound arterial hypotension—note the flattening of the EEG.

The elevated inferior caval pressure seen in the third line shows evidence of the cause. The EEG looks notably unhappy.

In the next record (Fig. 11), 2 minutes later, a fall in i.v.c. pressure and recovery of the arterial pressure is clearly seen to follow removal of the tape; only 2 minutes later the EEG and ECG have recovered considerably towards normal. At this moment protamine was given at an excessive rate, leading to profound hypotension, as seen in the second portion of Fig. 12; note that in 3 minutes the EEG has again flattened. Methedrine was given and only 1 minute later the EEG is seen to have recovered considerably; 2 minutes later it is normal. The final very satisfactory condition is seen in records 7 minutes later (Fig. 13): excellent activity of the EEG, satisfactory ECG. There is marked respiratory variation in caval and aortic pressures.

In our view, which is confirmed by the recent experience of others (Theye *et al.*, 1957), these EEG changes denote a fall in cerebral blood flow below a safe level and indicate appropriate prompt and effective treatment to ensure survival.

It is a pleasure to acknowledge my indebtedness to Mr. Charles Drew, Dr. Percy Cliffe and Dr. Douglas Pearce; also to Dr. Peter Hansell, Miss Jill Hassell and Miss P. Dawson.

## REFERENCES

ANDREASEN, A. T., and WATSON, F. (1952) *Brit. J. Surg.*, **39,** 548.
——, —— (1953*a*) *Brit. J. Surg.*, **41,** 195.
——, —— (1953*b*) *Ann. R. Coll. Surg. Engl.*, **12,** 261.
CLOWES, G. H. A., Jr. (1957*a*) *J. thorac. Surg.*, **34,** 589.
—— (1957*b*) *J. thorac. Surg.*, **34,** 716.
COHEN, M., and LILLEHEI, C. W. (1954) *Surg. Gynec. Obstet.*, **98,** 225.
DREW, C. E., CLIFFE, P., SCURR, C. F., FORREST, D. M., PEARCE, D. J., KING, P. A., COLES, H. M. T., LEVEAUX, V. M., and ZILVA, J. F. (1957) *Brit. med. J.*, ii, 1325.
GIANNELLI, S., Jr., MOLTHAN, M. F., BEST, R. J., DULL, J. A., and KIRBY, C. K. (1957) *J. thorac. Surg.*, **34,** 563.
HUDSON, A. (1958) *Proc. R. Soc. Med.*, **51,** 591.
KARLSON, K. E. (1957) *J. thorac. Surg.*, **34,** 716.
LIBET, B., FAZEKAS, J. F., MEIROWSKY, A. M., CAMPBELL, E. H., and HIMWICH, H. E. (1940) *Amer. J. Physiol.*, **129,** 404.
MELROSE, D. G., DREYER, B., BENTALL, H. H., and BAKER, J. B. E. (1955) *Lancet*, ii, 21.
PANETH, M., SELLERS, R., GOTT, V. L., WEIRICH, W. L., ALLEN, P., READ, R. C., and LILLEHEI, C. W. (1957) *J. thorac. Surg.*, **34,** 570.
THEYE, R. A., PATRICK, R. T., and KIRKLIN, J. W. (1957) *J. thorac. Surg.*, **34,** 709.

**Dr. John Beard:**

*The Anæsthetic Management of Patients for Extracorporeal Circulation*

We have heard two excellent papers on the theoretical aspects of the subject and I should have liked to have been able to give a simple practical account of anæsthesia for these cases. Unfortunately it is not yet quite like that, the whole affair still has much of "science fiction" about it. The apparatus is, even in its simpler forms, still complex. We must at this stage record many variables which will in the near future be unnecessary and the size of the team will be reduced as time goes on.

*Type of Case*

First, to consider the type of case suitable for the "heart-lung machine": At present the most clear-cut indication is the interventricular septal defect—not the small asymptomatic "maladie de Roger" but those large enough to have an appreciable left to right shunt.

UNIVERSITY OF MICHIGAN LIBRARIES

Here the left ventricle returns to the right ventricle part of its output which circulates round and round the pulmonary circuit. These cases are not cyanosed but have overloaded pulmonary circulation and are liable to frequent chest infections. The raised pulmonary artery pressures may be associated with changes in the lung vessels and an increased pulmonary vascular resistance. Once this has occurred, while the defect can be closed, convalescence will be more than usually difficult and the ultimate benefit doubtful. When the pulmonary artery pressure is equal to the systemic pressure, operation is not often indicated.

Atrial septal defects of uncomplicated types can be repaired by closed methods, by the "atrial-well" technique of Gross, or by open cardiotomy using hypothermia which allows the five to ten minutes of circulatory arrest needed. But it is at least possible that as by-pass practice improves even the most skilful surgeon will come to prefer more leisurely techniques which may be expected to lead to a higher percentage of successful closures. Congenital aortic, and simple pulmonary valve stenosis are reported to do well and Fallot's tetrad may now be treated by resection of the pulmonary stenosis and closure of the septal defect, the time needed for this more radical procedure being within the limits of the pump. Transposition of the great vessels is a more difficult problem and I do not know of any successes. Unfortunately the much more commonly seen cases of mitral and aortic incompetence also, with few exceptions, do badly.

This list is, of course, tentative, varying from centre to centre, and subject to modification with time and increasing experience.

*The flow rate*

Next the flow rate to be used must be decided. Our team works with the Melrose pump (*see* Fig. 2, page 581) which can give a high flow rate. This is best expressed as litres per square metre of surface area since metabolic need and cardiac output are more directly related to this than to body weight. We aim at about 2·4 litres per square metre per minute which corresponds to 120 ml./kg./min. in a child or 70 ml./kg./min. in an adult; the difference illustrating the difficulty of relating flow rate to body weight rather than to surface area. This flow is probably adequate but is less than the normal resting cardiac output which is about 3 l./sq.m./min. The difference is to some extent compensated by the anæsthetized and curarized state which lowers the metabolic needs as also does the fall in temperature consequent on cardiotomy and by-pass.

Many consider that a low flow rate involves oxygen lack in the tissues and hence allows anaerobic metabolism with the liberation of lactic or pyruvic acid. This metabolic acidosis can be compensated in some measure by deliberate overventilation, washing out carbon dioxide in order that a respiratory alkalosis may counter a metabolic acidosis. Those working with low flow rates therefore use 100% oxygen, and in order to secure adequate supplies of oxygen to the patient, tend to work with very high oxygen tensions (up to 500 mm.Hg) in the arterialized blood well above the physiological range, which may have serious disadvantages. When using high flow rates, on the contrary, it is usual to add carbon dioxide which aids the dissociation of oxyhæmoglobin, and it is, in general, possible to maintain the venous oxygen tension at a more nearly normal level without having to raise the arterial oxygen tension much above normal. Incidentally in such lesions as Fallot's tetrad the very large volumes of blood which pass through the bronchial arteries via the pulmonary veins into the heart during cardiotomy (even in selective cardiac arrest) need very high flow rates for their replacement.

*Premedication and Anæsthesia*

For premedication for these cases we use phenergan and pethidine; perhaps the phenergan in some measure reduces any febrile reactions to the massive blood transfusions involved. In these rather precariously balanced cases we give a test dose of pethidine a few days before operation recording the blood pressure to detect any unusually marked hypotensive response. For anæsthesia ether, cyclopropane and thiobarbiturate nitrous oxide sequences have all been employed by different groups. We use the latter largely because we are most accustomed to it for cardiac surgery and because of the explosion risk.

As soon as the patient is anæsthetized, but before curarization, he is weighed naked on scales accurate to 5 grams. This, repeated at the end of the operation with the allowance for weight of wound dressings, endotracheal and drainage tubes, is done as a check on blood replacement. It does not, however, exclude any blood lost into the pleural cavity or other extravascular loss and we are about to measure blood volumes using radio-active chromium. Two pleural drainage tubes are inserted as soon as the chest is open and any blood loss is led by negative pressure into a measuring cylinder where it can be easily seen by the anæsthetist: during operation the swabs are weighed and all blood losses continuously recorded as a graph as is also all fluid replacement, the "running totals" thus being instantly available for comparison.

When on the table, cannulæ are inserted into the aorta and inferior vena cava via the groin, and into the superior vena cava via the arm. The pressures are recorded photographically, inkwriters having insufficient travel to record the variations with sufficient accuracy. Needle electrodes are used for the electrocardiograph and electroencephalograph which are monitored by fluoroscope and inkwriter respectively. These various recordings serve to indicate the adequacy or otherwise of perfusion and are supplemented by clinical observation which includes the degree of conjunctival congestion, pupil size and the circulation in the retinal arteries by ophthalmoscopy.

Body temperature is measured by thermistors placed in the œsophagus behind the heart and in the nasopharynx, and controlled by a water mattress on the operating table through which water circulates at about 42° C. By this means we limit the fall due to cardiotomy and extracorporeal circulation to one or two degrees.

Before going on "by-pass" a generous dose of pethidine and perhaps more curare is given, as the level of anæsthesia is much lighter when the large volume of relatively acid blood from the machine is added to the circulation. This blood may also be less viscous than that in the body (especially in polycythæmic patients) so that vaso-pressors may be needed for maintenance of blood pressure. Similarly during and after perfusions a fall of blood pressure in the presence of adequate blood balance and of raised or normal venous pressure is treated by vasopressors, mephentermine being the current choice. Overtransfusion is most carefully avoided, the aim being to maintain body weight equal to or even very slightly less than the pre-operative weight.

Heart block may need treatment with isoprenaline or molar lactate, or if need be by an electrode, buried in the heart muscle, connected to Dr. Aubrey Leatham's stimulator. While on perfusion the lungs are held partially inflated by an oxygen-helium mixture, afterwards being inflated by a positive pressure machine with oxygen until nitrous oxide is needed.

[Here Dr. Beard showed a case which illustrated points in the post-operative care, in particular the increased comfort which may follow tracheotomy in patients who are unable to clear their secretions after a very major operation involving bilateral thoracotomy.]

**Dr. W. A. Hudson** (Birmingham):

*The Electro-encephalogram in Experimental Cardio-pulmonary By-pass*

Dr. Hudson said that in the Department of Surgery at the Queen Elizabeth Hospital they had performed, during the last six months, 37 chronic cardiopulmonary by-pass experiments on dogs with 22 fourteen-day survivals. Monitoring was achieved by continuous records of the electrocardiogram, aortic and inferior vena caval pressures, and the electro-encephalogram (EEG) to which he wished to refer. The electrodes used were tempered steel pins, varnished except for the points, which were lightly hammered into the skull of the anæsthetized dog in the parasagittal frontal and occipital regions. An optional earth electrode was similarly inserted in the mid-line in the region of the frontal sinus. The records had been free of interference and artefacts. No significant changes in the records in different dogs, or with different siting of the electrodes, were noticed.

A standard anæsthetic was used. The unpremedicated dog was induced with 10 mg. of thiopentone and 1 mg. of Scoline per kilogram of body-weight. Following intubation, anæsthesia was maintained with nitrous oxide and oxygen and increments of a quarter of the induction dose of barbiturate or relaxant as required. With this regime there had been no variation in the EEG, and any deterioration seen could therefore be assumed to be due to other causes, as, for example, anoxia, acidosis, cerebral congestion or hypotension.

Progressive deterioration of the EEG proceeded through 6 grades (Fig. 1). The top tracing, he suspected, was a convulsive record. Grade 1 was the tracing seen or aimed at in a satisfactory experiment. Deterioration proceeded via Grade 2 where the tracing showed an increase in amplitude and a fall in frequency to Grade 3 with a regular, large amplitude, slower frequency record. This passed to Grade 4 where large amplitude, very slow frequency waves were seen. These decreased in amplitude (Grade 5) and became interrupted by periods of zero voltage until all electrical activity ceased (Grade 6). He demonstrated slides, showing examples of these grades during by-pass, by-pass with potassium arrest, hypotension, asphyxia, and venous congestion. Assessment of the significance of these grades was empirical and incomplete. A cause was sought for deterioration beyond Grade 2 and Grades 4, 5 and 6 were considered to be ominous. Nevertheless, dogs had survived episodes of Grade 5 or 6 for periods up to 6 minutes.

He showed the EEG (Fig. 2) of a 17-year-old girl undergoing repair of atrial septal defect using hypothermia. The top record, when ether was being used, showed a Grade 4 EEG. The middle record, on nitrous oxide and oxygen, and at a lower temperature, showed a Grade 1 EEG. This suggested that EEG monitoring of a by-pass might be difficult if

UNIVERSITY OF MICHIGAN LIBRARIES

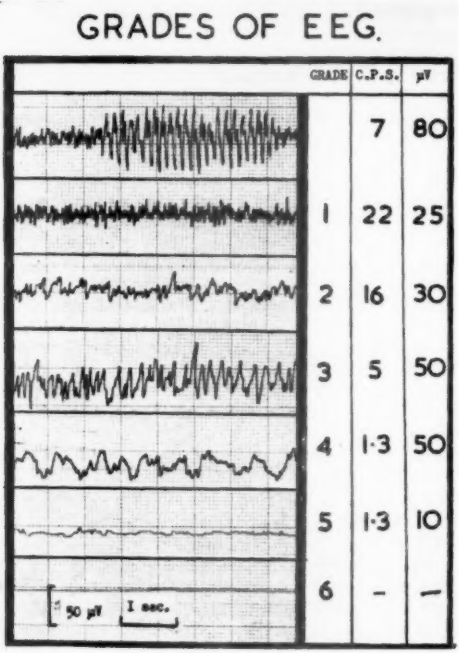



FIG. 1.

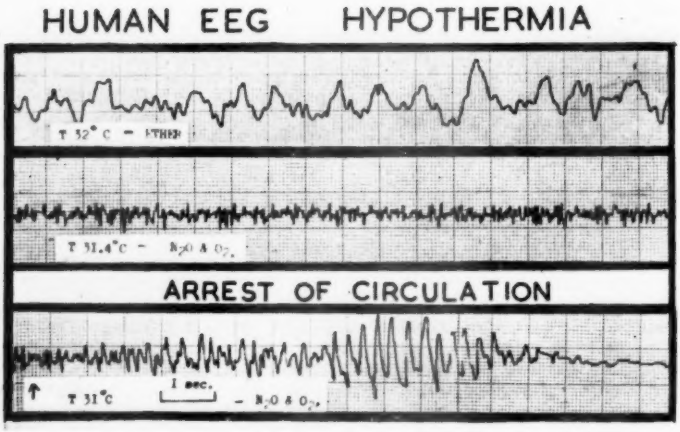



FIG. 2.

ether were used, as early EEG deterioration due to unsatisfactory perfusion might be obscured by the EEG changes of ether anæsthesia. The bottom record showed the EEG deterioration when the circulation was interrupted prior to cardiotomy. The arrow indicated aortic clamping. Within 15 seconds, the EEG had deteriorated through the grades described to Grade 6. The circulation was arrested for 5 minutes. EEG recovery began 3 minutes later when Grade 5 appeared and had reached Grade 1 three hours later, at which time the patient, whose temperature was then 35° C., responded to questions.

Dr. Hudson concluded by suggesting that this electroencephalographic monitoring technique could be applied to human cardiopulmonary by-pass.

# Clinical Section

President—E. W. RICHES, M.C., M.S., F.R.C.S.

[*March* 14, 1958]

**Carcinoma of Pancreas.**—PAUL T. SAVAGE, M.B., F.R.C.S.

Male, aged 59.

*History.*—He was perfectly well until ten days previously, when he complained of a pain in his upper abdomen, which has become more severe since. Appetite normal; bowels open regularly; no urinary symptoms.

*Physical examination.*—Healthy looking man of 59. The only relevant abnormality was a slightly tender, large spherical mass 8 in. in diameter moving on respiration and situated in the right hypochondrium. The upper border of the mass could easily be defined and it could be pushed into the left loin and palpated bimanually. It was dull to percussion.

*Investigations.*—Hæmoglobin 76%. W.B.C. 7,700 (72% polys.).

I.V.P. shows good excretion from both kidneys. No displacement of left kidney and no abnormality of pelvi-calyceal system. The gas shadow of the colon shows downward displacement of the splenic flexure.

Barium meal shows a large filling defect of the greater curve of the stomach, but the mucosal pattern over this appears to be normal.

Follow-through again showed downward displacement of the splenic flexure of the colon which appears otherwise normal.

Gastroscopy: The gastroscope could be felt to slide over a solid mass in the region of the greater curvature of the stomach. A good view of the upper part of the body of the stomach was obtained. The mucosa over the lesion appeared to be devoid of folds, but there was no evidence of ulceration or carcinoma. The antrum and pylorus could not be visualized.

*Progress and treatment.*—A clinical diagnosis of leiomyoma of the stomach was made, and operation advised.

*Operation*, 21.1.58 (Mr. Savage).—12 in. upper mid-line incision, later enlarged by "T" cut into left flank. A huge, fairly well-encapsulated neoplasm was found lying between the stomach and the transverse colon. The body of the stomach and the transverse mesocolon were spread out over it. The mesocolon was clearly invaded by growth, as was the pyloric end of the stomach. The spleen and stomach were dislocated up out of the abdomen, and the neoplasm seen to be replacing the body and tail of the pancreas. The tumour mass was removed, together with the involved pyloric end of the stomach, transverse colon and mesocolon and spleen. Continuity of the alimentary tract was restored by end-to-end anastomosis of the colon and a gastro-duodenal (Billroth I) anastomosis. Convalescence was uneventful.

*Pathological report.*—Partly encapsulated undifferentiated polygonal cell carcinoma of pancreas, showing many mitotic figures and very little fibrous tissue. No secondaries in any of the lymph nodes in the resected specimen. Neoplastic cells seen in dilated blood spaces in capsule of lesion.



UNIVERSITY OF MICHIGAN LIBRARIES

**Phæochromocytoma.**—W. W. DAVEY, M.D., F.R.C.S., F.R.C.S.I.

Mrs. F. M., aged 47. Admitted to the Whittington Hospital under Dr. A. L. Jacobs (15.11.57).

*History.*—Two years' throbbing headache. Four months' defective vision. Fairly sudden onset. General weakness and tiredness. Vague abdominal pains and palpitations. Some sweating and spells of faintness but is not very definite about this.

*Previous history.*—March 1956: E.C.T. for endogenous depression. December 1956 to February 1957: In-patient for duodenal ulcer. Hypertension noted at that time.



FIG. 1.

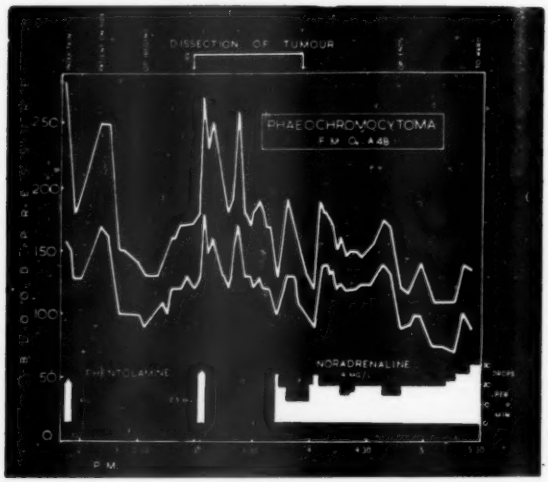



FIG. 2.



FIG. 1.—Retrograde pyelogram. Depression of upper calyces.

FIG. 2.—Control of blood pressure during removal of phæochromocytoma.

FIG. 3.—Specimen of phæochromocytoma, weighing 353 grams.



FIG. 3.

*On examination.*—Blood pressure 230/155. Apex beat sixth space just outside the mid-clavicular line. Fundi: extensive retinopathy with exudates and hæmorrhages. Right kidney easily palpable.

*Investigations.*—After phentolamine 5 mg. i.v. the blood pressure fell from 220/130 to 150/95. Urinary pressor amines: 1·0 μg./ml. urine noradrenaline. Straight X-ray genito-urinary tract: rounded shadow above right kidney. Retrograde pyelogram: depression of upper calyces right side (Fig. 1). Tomography confirms presence of large rounded tumour above right kidney.

*Operation* (2.1.58).—Right abdomino-thoracic incision with excision of tenth rib. Mobilization of tumour. One artery and two large veins tied. Removal of tumour. Left suprarenal palpated and considered to be normal.

The blood pressure rose to 290/160 during the induction and 2 mg. phentolamine were given. The pressure remained below 250/150 till the tumour was being handled at which point it reached 280/170 and a further 2·5 mg. phentolamine was given (Fig. 2). After operation the systolic blood pressure was kept above 130 using a noradrenaline i.v. drip (4 mg./l). It was found possible to discontinue this at the end of twenty-six hours but small quantities had to be used periodically for the next thirty-six hours before "weaning" was complete.

*Progress.*—Her symptoms have almost disappeared and she can once more read the scale of the weighing machine in her confectioner's shop.

*Comment.*—Right abdomino-thoracic incision is strongly advised; it makes the operation simple, safe and non-traumatic.

The use of phentolamine is probably unnecessary. A straight X-ray was sufficient to decide on which side the tumour was placed. The tumour weighed 353 grams and is one of the largest removed in this country (Fig. 3). The patient's blood pressure has risen to 180/110 since operation—probably an index that the condition had existed for a long time.

**Tracheo-œsophageal Fistula Without Atresia.**—R. H. FRANKLIN, F.R.C.S.

A. C., male, born on November 10, 1955, after a normal pregnancy. The birth weight was 6 lb. 11¾ oz. and the delivery was normal. When he was 4 days old he developed pneumonia, which was treated with Aureomycin and oxygen, and the condition improved and cleared up in a fortnight.

On January 17, 1956, he was readmitted to hospital with the story that he had had continuous attacks of coughing and difficulty in taking feeds. On examination at this time he was found to have scattered râles at the right base and rhonchi all over both lungs. A provisional diagnosis of bronchiolitis was made and he was treated with Terramycin and tube feeding, and he improved on this regime. He was an ill-looking child at this stage and normal feeding produced a recurrence of his chest signs and his abdomen was distended. It looked as though he was gradually going downhill.



FIG. 1.—Opaque swallow showing tracheo-œsophageal fistula without atresia.

Fortunately the parents had chosen as godfather for the child a thoracic surgeon, Mr. L. L. Bromley. He realized that there must be some cause for the repeated attacks of pneumonia and examined the child with the object of excluding some condition such as pharyngeal pouch which might be causing aspiration of the feeds. He passed a catheter into the stomach with ease and he was about to abandon the diagnosis of a pharyngeal or an œsophageal abnormality, when he noticed that a considerable quantity of air came out of the catheter. He left it in position in the hope of relieving the child's distension. After some time, air was still coming out so he thought of the possibility of a fistula between the œsophagus and trachea. The child was given an opaque swallow (aqueous propyliodone) and this showed a tracheo-œsophageal fistula at the level of the second thoracic vertebra (Fig. 1). At this stage I was asked to see the child. He looked extremely ill and was obviously hungry although not dehydrated. The abdomen was grossly distended and hyper-resonant. Scattered râles were present over the whole of the right chest and the percussion note was diminished. Air entry was good. A chest X-ray showed collapse of the right base and consolidation in the anterior segment of the right upper lobe.

On January 23, 1956, a Kader-Senn gastrostomy was carried out under local anæsthesia. With gastrostomy feeds, antibiotics and postural drainage for his chest, he gradually improved and on February 9, 1956, an operation was undertaken to correct the deformity.

UNIVERSITY OF MICHIGAN LIBRARIES



FIG. 2.—Infant, six months after operation for tracheo-œsophageal fistula.

Under general anæsthesia the chest was opened through an incision in the fifth right intercostal space. A few minutes were spent in massaging air gently into the collapsed parts of the lung. The vena azygos arch was ligatured and divided and a search made for the fistula by separating the trachea from the œsophagus at the level of the second thoracic vertebra. It was rather difficult finding the fistula as the opening was higher than expected; it passed obliquely downwards from the trachea to the œsophagus. On dividing the fistula the opening was seen to be ¼ in. in diameter. The opening into the trachea and that into the œsophagus were both closed with interrupted sutures of 5/0 silk. A little saline was introduced into the thorax to test the effectiveness of the closure. An underwater intercostal drain was introduced, the lung fully expanded and the chest closed.

Following this operation the child made an uneventful recovery (Fig. 2) and has had no trouble with his feeds or with his chest since. There appears to be no evidence of any other congenital abnormality.

This condition has always been regarded as one of the greatest rarity. A case was described by Imperatori in 1939 in a boy 6 years of age, the son of a doctor. Here the fistula was high and was repaired by a transcervical transtracheal route. Other reported cases include Helmsworth and Pryles (1951) where the patient was operated on at the age of 6 months on the third admission to hospital. In this instance barium swallows and bronchoscopy had failed to demonstrate the fistula. Robb (1952–53) reported a patient who had a co-existing pouch operated on at the age of 11 years. Mullard (1954) described two patients, both of whom were aged 54 years. It is interesting to note that Negus (1929) showed a specimen of the œsophagus of a man, aged 45 years, with a tracheo-œsophageal fistula, the patient having died of carcinoma of the lung.

From the reported cases it is clear that the abnormality is consistent with survival and, in fact, symptoms may only be produced when the patient is in certain positions, and the size and direction of the fistula may be such that solid food takes the proper channel and only fluids find their way through the fistula into the trachea. It is also clear that diagnosis is difficult but that the condition is probably much commoner than is generally believed. A number of infants may be lost as the result of recurrent chest complications and in these the presence of a fistula may remain undiagnosed even at autopsy. The characteristic symptoms and signs in an infant are as follows: feeding may produce coughing, choking and cyanosis. This may be worse with liquids than with solids. In the newborn infant these symptoms immediately suggest an œsophageal atresia, but this diagnosis is eliminated by the free passage of a catheter into the stomach. Auscultation of the infant's lungs before and immediately after feeding may be most suggestive. The appearance of marked abdominal distension, particularly when the infant cries, is a common feature. Feeding by means of a gastric tube usually produces an improvement. In some cases the signs and symptoms are less dramatic and the picture is merely that of an infant who has recurrent attacks of pneumonia for no apparent reason. This clinical picture should always arouse the suspicion of a tracheo-œsophageal fistula and determined efforts should be made to establish the diagnosis. The condition differs from congenital atresia of the œsophagus where the diagnosis is perfectly easy once the possibility has been considered. In the case of a fistula without atresia, this is not so and an opaque swallow may have to be carried out in several positions before the fistula is demonstrated. Bronchoscopy may reveal the opening in the trachea, but again, if the opening is small and covered by a hood of mucous membrane, it may be difficult to find. Elaborate methods of diagnosis have been suggested such as introduction of air or dye into the trachea and simultaneous observation made through the œsophagoscope, but the important point is to remember the possibility of the condition and once this has been raised to make every effort to confirm the diagnosis.

## REFERENCES

HELMSWORTH, J. A., and PRYLES, C. V. (1951) *J. Pediat.*, **38**, 610.
IMPERATORI, C. J. (1939) *Arch. Otolaryng., Chicago*, **30**, 352.
MULLARD, K. S. (1954) *J. thorac. Surg.*, **28**, 39.
NEGUS, V. E. (1929) *Proc. R. Soc. Med.*, **22**, 527.
ROBB, D. (1952–53) *Aust. N.Z. J. Surg.*, **22**, 120.

[*May* 9, 1958]

## Meeting at the Canadian Red Cross Memorial Hospital, Taplow, Maidenhead

**The Eye Changes of Still's Disease: Two Cases Illustrating Treatment.**—W. K. Smiley, M.B., D.O.M.S., F.R.C.S.

I.—K. G., male, aged 18, a Jamaican.

His joints became involved at the age of 7 years; eyes became affected three years later. Treated for a time in Jamaica and transferred to a London hospital about a year ago. First seen in this Unit six months ago. He is on the Blind register.

Right eye on admission showed the typical "ocular triad" of Still's disease, i.e. insidious

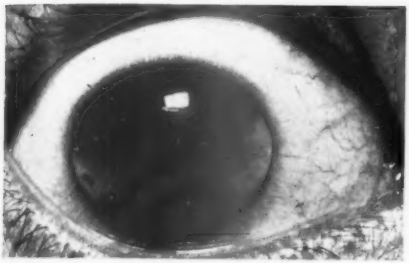


Fig. 1.—Iridocyclitis, corneal band opacity and complicated cataract in Still's disease.

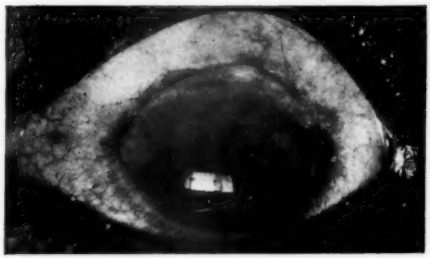


Fig. 2.—Phthisis bulbi following acute exacerbation of iridocyclitis after a needling operation for cataract.

iridocyclitis, corneal band opacity and complicated cataract (Fig. 1). Vision = perception of hand movements. Treatment has consisted of:

(1) Mydriatics and local and systemic cortisone to control the iridocyclitis.

(2) Dispersal of the central part of the superficial calcareous corneal band by chelation.

*Comment.*

Chelating agents are compounds which combine with various metallic ions, such as calcium in this case, to form soluble complexes, thus removing them from their chemical environment.

A 0·01 M. solution of sodium versenate (disodium ethylenediamine-tetra-acetic acid) is used as a contact bath applied to the cornea for fifteen minutes after thorough removal of the epithelium overlying the band opacity by curettage. Calcium salts are readily abstracted in this period and the eye is then bandaged after instillation of an antibiotic. The corneal epithelium is completely regenerated in two or three days.

(3) Complete iridectomy to facilitate the subsequent removal of the cataract and to test the reaction of the eye to surgery.

The final step remains:

(4) Removal of the cataract to restore useful vision. That this can be hazardous is shown by the condition of the other eye. Left eye was similarly involved and is now permanently blind and shrinking, following needling of cataract at another hospital with subsequent exacerbation of inflammation (Fig. 2).

II.—B. J., male, aged 18.

Joints became involved at the age of 9 years; right eye developed insidious iridocyclitis two weeks later and the left eye suffered a most acute attack one year and nine months afterwards.

When first seen in this Unit in 1949, the iridocyclitis in the right eye had subsided but a band opacity and cataract were already established. His left eye was then normal. When readmitted one month after the onset of the acute iridocyclitis the left vision was reduced to perception of hand movements by gross inflammatory exudate in the vitreous. This eye also developed a band keratopathy and a complicated cataract. In July 1951 he was put on the Blind register and in October 1951 he went to a Blind school.

UNIVERSITY OF MICHIGAN LIBRARIES

In the last seven years he has undergone nine operations for dispersal of the cataracts (Figs. 3 and 4) and chelation of the corneal band opacities (Figs. 5 and 6). His vision with glasses is now right eye 6/24 and left eye 6/9. He is no longer on the Blind register and is a full-time student at a College of Art.

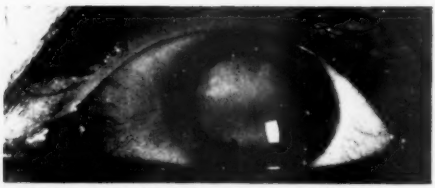


FIG. 3.—Complicated cataract in Still's disease.

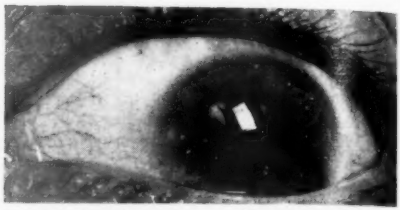


FIG. 4.—The same eye after dispersal of cataract by repeated needling.

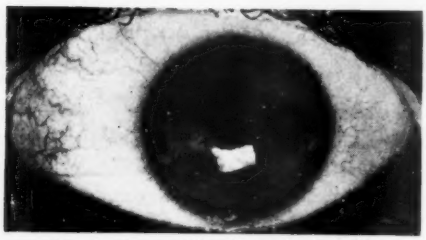


FIG. 5.—Corneal band opacity in Still's disease.

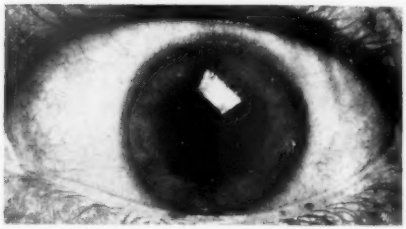


FIG. 6.—The same eye after chelation of calcium from corneal band opacity with sodium versenate.

*Comment.*—In the last eight and a half years in this Unit, we have examined the eyes of over 200 children under the age of 16 with Still's disease and have found 12 with iridocyclitis. This is the primary lesion and is characteristically insidious and symptom-free in the early stages. It may involve one or both eyes and is unrelated to age, sex or the severity and duration of the arthritis. Later in 50% of our cases some degree of corneal band opacity occurred and in 25% a complicated cataract developed. Three of our cases have been, or are still, on the Blind register.

The two cases shown illustrate the problem and its management, which has been discussed in more detail by Smiley *et al.* (1957).

REFERENCE

SMILEY, W. K., MAY, E., and BYWATERS, E. G. L. (1957) *Ann. Rheum. Dis.*, **16**, 371.

**Polyarteritis Nodosa and Hydronephrosis.**—G. S. WAKEFIELD, M.R.C.P. (for Professor E. G. L. BYWATERS, F.R.C.P.), and RAYMOND RAMSAY, M.B.E., F.R.C.S.

A. I., female, aged 21.

Asthma from age of 16. In September 1956 she developed patchy hypalgesia and weakness of her forearms and hands, feet and lower legs, and rapidly lost 1 stone in weight, with malaise, anorexia and dyspnœa at rest.

*On examination.*—Generalized livido reticularis. Central nervous system normal. Peripheral neuritis of all four limbs with foot-drop and hamstring contractures. Enlargement of liver and spleen. Dependent œdema. Raised venous pressure. Blood pressure 135/110. No cardiac enlargement. Mitral pansystolic murmur. Impaired breath sounds with crepitations left base.

*Investigations.*—Hb 106%. W.B.C. 18,400 (eosinophils 50%). E.S.R. 36 mm. in 1 hr. (Westergren). Bone marrow: hyperplastic eosinophil series. No L.E. cells. Coombs test negative. Urine: R.B.C. ++; *B. coli* on culture. Blood urea 64 mg.%. ECG normal. Chest X-ray: bilateral pleural effusions. *Muscle biopsy:* no evidence of arteritis.

*Course.*—She was treated with ACTH and later prednisone. Her cardiac failure persisted and she developed a severe bronchopneumonia which responded slowly to antibiotics. After recovery from this, she made satisfactory progress and her blood pressure has since been normal. The signs of peripheral neuritis receded and her contractures were treated by serial plasters. Her mitral incompetence was unchanged. In March 1957 she suffered for the first time from severe left loin pain and ureteric colic. I.V.P. showed doubtful clubbing of left

renal calyces. Urine culture grew *Staph. aureus* sensitive to Chloromycetin. A course of this and other antibiotics failed to eradicate the infection. She was discharged from hospital on prednisone and digitalis, able to lead a near-normal life. Attempts to lower the steroid dose resulted in recurrences of the peripheral nerve lesions.

In March 1958 she suffered a severe exacerbation of her urinary infection associated with ureteric colic which resulted in her readmission when urine culture again grew a *Staph. aureus*. Repeat I.V.P. showed an obvious left hydronephrosis and a surgical opinion was sought.

Bilateral retrograde pyelography showed a normal right kidney: urine from the right ureteric catheter showed no abnormality. Urine from the left ureteric catheter grew *Staph. aureus*. In particular, the left ureteric catheter could not be passed beyond the brim of the pelvis (*see* Fig. 1). Injection of dye up the catheter failed to pass this point. It was thought probable that the hydronephrosis was due to a stricture of the ureter at this point.



FIG. 1.




FIG. 2.

*Operation* (17.4.58).—The left ureter was explored, using a Stockholm incision. At the brim of the pelvis the ureter was surrounded by periureteral fibrosis which, on dissection, displayed an almost complete stenosis of the ureter. Proximal to the stricture the ureter was greatly dilated (about 2·5 cm. in diameter). Distally the ureter was completely collapsed (*see* Fig. 2). The stricture was dilated and a very small-bore rubber T-tube was placed in situ.

*Post-operation.*—The T-tube was removed four weeks after operation. There was no urinary discharge from the wound and the fistula closed two days later. An I.V.P. twenty days after the operation shows the hydronephrosis greatly reduced and the function of the left kidney much improved. She has remained entirely free from symptoms but her urine still contains *Staph. aureus*.

UNIVERSITY OF MICHIGAN LIBRARIES

**Encephalomyelitis due to Virus B.**—PHILIP H. WILLCOX, M.D., M.R.C.P.

B. T., male, aged 31.

A laboratory assistant at a research laboratory, where he cared for monkeys used for work on virus diseases. He had been inoculated for poliomyelitis on July 18 and August 23, and for influenza on October 3, 1957. On September 22 he was bitten on the right hand twice, once by a rhesus and once by a cynomolgus monkey. Only small superficial wounds were caused and quickly healed; no subsequent vesiculation at the site of the lesions.

His illness started with fever and headache on 12.10.57 which at first was thought to be influenza; on 14.10.57 when his left leg became weak and he developed retention of urine, poliomyelitis was suspected. He was admitted to Maidenhead Isolation Hospital on 15.10.57 with weakness of left lower leg and on 17.10.57 he developed complete flaccid paralysis of his legs and left arm, with absent reflexes. There was loss of sensation to pain and touch over a wide area of the left leg and the dorsum of right foot, back stiffness and muscular weakness of the trunk and abdominal muscles including diaphragm.

*C.S.F.*—Red cells 5, leucocytes 75/c.mm., 95% lymphos, 5% polymorphs. Protein 80 mg.%, chlorides 680 mg.%. No organisms.

On 17.10.57 he was restless and unable to sleep and vomited several times though there was no headache. Twitching of facial muscles and tremor of tongue. Cranial nerves normal. Considerable weakness of left arm, involving wrist, triceps, biceps and deltoid, with feeble reflexes. Right arm showed less extensive paralysis and very brisk reflexes. Almost complete flaccid paralysis of legs and sensory loss as already mentioned.

On 18.10.57 he was transferred to the South Middlesex Hospital owing to involvement of respiratory muscles and was put in a tank respirator. He was later treated with positive pressure after tracheotomy. His temperature ranged from 102° to 103° F. but subsided to normal within two weeks, with improvement in general condition and the paralysis of the right leg and swallowing. By 29.11.57 there was marked improvement especially of right arm and leg and on 9.12.57 positive pressure was discontinued. Retention of urine cleared up and the infection of bladder was treated.

Since December he has showed steady and gradual improvement but there is spastic weakness of both lower limbs, worse on left, with tremors and rigidity and residual weakness of the left wrist and hand including small muscles. There is sensory loss of little finger of left hand and some nystagmus remains. He is now learning to walk with a caliper on his left leg at a rehabilitation centre. Virus research by Dr. W. Wood of Glaxo Laboratories did not reveal proof of virus B infection in blood or fæcal specimens taken on 17.10.57, but there was increased serum antibody to virus B (Sabin and Wright).

*Diagnosis.*—Encephalomyelitis due to virus B (Sabin and Wright, 1934) contracted from monkey bites on 22.9.57.

*Comments.*—The diagnosis was at first thought to be poliomyelitis with progressive ascending paralysis of limb and trunk muscles, commencing in the legs. The likelihood of bulbar involvement necessitated treatment with positive pressure respiration and tracheotomy.

The first recorded case of virus B encephalomyelitis occurred in 1932, in a doctor bitten by a rhesus monkey. Sabin and Wright (1934) isolated in rabbits a virus from brain material of this fatal case which closely resembled the virus of herpes simplex and was designated "Virus B". According to Rivers (1952), only 4 fatal cases have been recorded, since that time, until 1952. Study of case records of the disease shows that the illness is similar in all cases to the present one and that death occurs from brain-stem involvement and respiratory paralysis. In this respect the disease resembles severe poliomyelitis and requires treatment on similar lines but the involvement of the sensory system and the history of the monkey bites excluded this diagnosis in the present case. As far as can be ascertained this is the first case known to have recovered, though there may have been other unrecorded cases.

The work of Wood and Shimada (1954) has shown that Virus B sometimes contaminates pools of poliomyelitis virus which is prepared in cultures employing tissue from both rhesus and cynomolgus monkeys and that the animals are quite healthy at the time of operation. Virus B infection causes in monkeys no demonstrable illness except transient ulcers in the mouth and the virus is probably present in the saliva of affected animals. A feature of the illness in the first case recorded by Sabin was a vesico-pustular lesion at the site of the bite but in the present case no such lesion occurred. In the second case reported by Sabin (1949), there was no history of a monkey bite and infection was presumed to have entered the body from a laceration of the hand infected with monkey saliva.

REFERENCES

RIVERS, T. M., ed. (1952) Viral and Rickettsial Infections of Man. 2nd ed. Philadelphia, p. 250.
SABIN, A. B. (1949) *J. clin. Invest.*, **28**, 808.
——, and WRIGHT, A. M. (1934) *J. exp. Med.*, **59**, 115.
WOOD, W., and SHIMADA, F. (1954) *Canad. J. publ. Hlth.*, **45**, 509.

# Section of the History of Medicine

President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., C.B., M.A., D.M., F.R.C.P.

[*May* 7, 1958]

## Alexander Pope: Poet and Cripple, 1688–1744

By Sir ARTHUR SALUSBURY MACNALTY, K.C.B., M.A., M.D.Oxon, F.R.C.P., F.R.C.S.

OF all exemplars of genius in conflict with bodily ills none waged a more ceaseless battle throughout the whole of life than Alexander Pope. Let us first survey his life and see what he accomplished.

### EARLY LIFE AND EDUCATION

Alexander Pope was born of elderly parents in Lombard Street, London, on May 21, 1688. They were Roman Catholics. His mother was Edith, daughter of William Turner of York. His father was a linendraper who made a fortune and retired to Binfield, near Windsor. Pope received a desultory education, partly from priestly tutors. He was for a short time a pupil at a Roman Catholic school at Twyford, near Winchester, from which, it is said, he was expelled for writing a lampoon on his headmaster, and then for a further brief period at a school near Hyde Park Corner. He was a born poet. "I lisped in numbers for the numbers came." As a boy he was called "the little nightingale" from his melodious voice. From the age of 12 he was practically self-taught and, though never a profound scholar, had a fair knowledge of Latin and Greek. In early youth he asked to be taken to Will's coffee-house to gaze on Dryden. By 1704 his verses received praise from several men of letters including William Wycherley, who persuaded the young poet to polish his own writings, until offended by Pope's trenchant criticisms.

### LATER LIFE AND FAME

*The Pastorals*, *The Essay on Criticism*, *Windsor Forest* and the *Rape of the Lock*, which was published in 1714, secured Pope fame and universal recognition as a great poet. In spite of ill-health, his industry was indefatigable and his literary output continuous. His translation of the *Iliad* (1715 to 1720) was very popular and brought him £5,000. Bentley's phrase: "a pretty poem, Mr. Pope, but you must not call it Homer," expressed the view of classical scholars, but, nevertheless, it is a distinguished English poem. Dr. Johnson termed it "the noblest version of poetry the world has ever seen"; Gray averred no other translation would ever equal it, and Gibbon said that it had every merit but that of faithfulness to the original. Pope followed up this success by translating the *Odyssey* (1725 to 1726), assisted by Broome and Fenton. This increased his fortune to £8,000 and made him financially independent.

In 1716 Mr. Pope, Senior, sold Binfield and the Pope family moved to Chiswick. Here Pope prepared a collected edition of his poems. In 1718, his father having died aged 75, he went with his mother to live at Twickenham, where his celebrated villa, grotto and grounds were visited by his friends, the leading men of letters, wits, statesmen and beauties of the day. With Dean Swift and others Pope wrote the *Miscellanies* (1727–28) and independently the *Dunciad* (1728–29), a savage satire on the critics and poetasters who had attacked him. From 1731 to 1735 Pope wrote his *Epistles*, and in 1733 he published his famous *Essay on Man*. On June 7 of that year his mother, whom he had looked after with filial devotion for many years, died at the advanced age of 93. Pope's last works were his *Imitations of Horace* (1733–39) and the fourth book of the *Dunciad* (1742).

*Place in poetry.*—Pope was the most famous poet of his time and was skilled in verse and the heroic couplet. There is no question that he is to be regarded as a true poet. He was a master of wit and satire and used these talents ruthlessly and often treacherously. His poetry is full of lines that are quotable and almost proverbial. *The Essay on Man*, for which Bolingbroke supplied the pseudo-philosophy, won for him a European reputation and was greatly admired by Voltaire. He had the art of crystallizing in terse verse those thoughts which are often in men's minds concerning the great problems of man's life and future destiny.



UNIVERSITY OF MICHIGAN LIBRARIES

*Friendships.*—Among Pope's intimate friends were Congreve, Gay, Dr. Arbuthnot, Addison, Steele, Dean Swift, Lord Peterborough, Lord Burlington, Spence and Bishop Warburton. In the last years of Queen Anne's reign, Dean Swift and Dr. Arbuthnot with the younger wits, Pope, Gay and Parnell, formed a little society called the Scriblerus Club, Martinus Scriblerus being the name of an imaginary pedant, a precursor of Scott's Dr. Dryasdust. They planned a joint-stock satire to be directed against "the abuses of human learning in every branch", and, according to Pope (Spence's *Anecdotes*), Atterbury, Congreve and Addison were also to collaborate. The scheme was abandoned but fragments of the satire were included in the *Miscellanies*. *The Memoirs of Martinus Scriblerus*, published in the quarto edition of Pope's works in 1741 were written mainly if not exclusively by Arbuthnot.

Dean Swift came over from Ireland in the summer of 1726 bringing *Gulliver's Travels* with him for which arrangements were made for publication by Pope. Swift, Arbuthnot, Gay and Pope agreed to publish a Miscellany to which Swift contributed verses. Two volumes of this work were brought out in June 1727. The third volume of the *Miscellanies* appeared in 1728 and a fourth in 1732. In Pope's amusing treatise on Bathos, a sarcastic description of bad authors in the third volume, he was helped by Arbuthnot.

Swift again visited England in April 1727 and stayed with Pope at Twickenham. The visit was not a success. "Two sick friends", says Swift in a subsequent letter, "never did well together." Swift in bad health left hurriedly and returned to Ireland. The two friends never met again.

Hypersensitive and subject to morbid vanity, Pope often imagined his friends were slighting him, quarrelled with them and scarified them in mordant satire. Thus the *Prologue to the Epistles*, addressed to Arbuthnot, has an ungrateful attack on Addison under the name of "Atticus". Pope never married, but like Sterne he had many sentimental friendships with women. He affected the society of the maids of honour. In 1714, he writes, "I went by water to Hampton Court, and met the Prince, with all his ladies on horseback, coming from hunting. Mrs. Bellenden and Mrs. Lepell took me into protection, contrary to the laws against harbouring Papists, and gave me a dinner, with something I liked better, an opportunity of conversing with Mrs. Howard. . . . Mrs. Lepell walked with me three or four hours by moonlight, and we met no creature of any quality but the King, who gave audience to the Vice-Chancellor all alone under the garden wall".

The poet posted away, "heartily tired" after this long moonlight walk.

From boyhood the poet was a friend of the two fair sisters, Teresa and Martha Blount who lived at Mapledurham, near Binfield. Teresa was at first his favourite, but his friendship with Martha was the more enduring. In Pope's latter years she lived with her mother near him at Twickenham and saw him daily; he left her a large share of his fortune. Many other ladies of the day were sorry for him, liked him for his wit and engaged in a quasi-sentimental correspondence with him. Among these was Lady Mary Wortley Montagu, who encouraged inoculation against smallpox in England, and collaborated with Pope in writing verse; but she only laughed at his presumption when the crooked little man made love to her. In revenge, Pope lampooned her brutally and unforgivably.



Mansell Collection

FIG. 1.—Alexander Pope.

*Appearance.*—Sir Joshua Reynolds gave the following description of Pope:

> "He was about four feet, six inches high, very hump-backed and deformed. He wore a black coat, and, according to the fashion of the time, had on a little sword. He had a large and very fine eye, and a long handsome nose; his mouth had those peculiar marks which are always found in the mouths of crooked persons; and the muscles which ran across the cheek were so strongly marked that they seemed like small cords."

Wycherley speaks of Pope's "little, tender, crazy carcass".

### Illnesses

As already observed, Pope was a martyr to ill-health throughout life. He was never completely well for many days together. Yet his spirit was indomitable and his industry immense. He spoke of his Muse as helping him through that "long disease, his life".

*Rickets.*—In childhood he suffered severely from rickets, being humpbacked through spinal curvature. He was protuberant before and behind and compared himself to a spider. As one of his sides was also contracted (*vide infra*), the condition seems to have been a kyphoscoliosis. He was brutally abused for his deformity by Dennis and others, and to the sense of his physical deformity may be ascribed much of the bitterness in his poetry and his spitefulness. His father also was humpbacked.

Pope frequently assumed the *nom de plume* of "Martinus Scriblerus" in writing his attacks on adverse critics. One of his many enemies founded on this the title of the "Martiniad", a counterblast to his *Dunciad*, giving the following cruel portrait of Pope's deformity:

"At Twickenham, chronicles remark,
There dwelt a little parish clerk,
A peevish wight, full fond of fame,
And Martin Scribbler was his name;
Meagre and wan and steeple-crown'd,
His visage long and shoulders round;
His crippled corpse two spindle-pegs
Support, instead of human legs;
His shrivelled skin's of dusky grain,
A cricket's voice and monkey's brain."

*Migraine.*—For many years Pope was subject to attacks of migraine, a weakness which he inherited from his mother. In 1728 he told Bathurst that he had the headache for four days in the week and was sick for the other three! To ease the attacks he took frequent cups of coffee which had to be prepared for him day and night. Caffeine with phenacetin sometimes is found beneficial in migraine to-day. Dr. Johnson says that Pope also found relief by inhaling the steam of hot coffee. He pampered his appetite by highly seasoned dishes and was fond of potted lampreys. He would always get up for dinner, in spite of headache, when these were provided.

*Delicacy and activity.*—At the age of 15 years Pope worked so hard in London at French and Italian, that his fragile health broke down and he despaired of recovery. The Abbé Southcote applied for advice to the celebrated Dr. Radcliffe who prescribed return to Binfield, horse exercise and freedom from work. Inder this regime Pope recovered; and showed his gratitude twenty years later by obtaining for Southcote through Sir Robert Walpole the headship of a rich abbey in France.

Johnson tells us that the poet was so weak as to be unable to rise to dress himself without help. He was so sensitive to cold that he had to wear a kind of fur doublet under a coarse linen shirt; one of his sides was contracted and he could scarcely stand upright till he was laced into "a boddice made of stiff canvas"; his legs were so slender that he had to wear three pairs of stockings, which he was unable to draw on and off without help. His seat had to be raised to bring him to a level with common tables. In the intervals of illness, he was remarkably active, paying frequent visits to London either by water or by road, staying with titled friends, taking the waters at Bath and riding to Oxford on many occasions. In later days he used a carriage and appeared once in Spence's rooms at Oxford "dreadfully fatigued", having chivalrously lent his chariot to a lady who had been hurt in an upset, and having walked three miles to the city through the heat of a summer day.

Pope tells us that when he went to London by water or to visit friends on the river he sat in a sedan-chair in the middle of the boat to keep his legs and his body comfortable. In a letter to Gay of date September 11, 1722, he wrote: "I think it obliging in you to desire an account of my health. The truth is I have never been in a worse state in my life and find whatever I have used as a remedy so ineffectual that I give myself entirely over." But, nevertheless, his resilient spirit triumphed over his bodily afflictions.

*Fever and rheumatism.*—Pope suffered occasionally from febrile attacks which may have been influenza or ague. In May 1710 he tells H. Cromwell that he is recovering from a serious illness contracted in town, but in a later letter in October he speaks of his "almost continued illness". In June 1717 he informed the Hon. Robert Digby that he "is not so much recovered from a fit of sickness as thinking of using your physicians, that is, asses' milk", which he ridiculed Lord Hervey (Sporus) for taking, terming him "a mere white curd of asses' milk" (*Epistle to Arbuthnot*). In 1722–23 (letter to Digby) he complained of having had a fever for six to seven days followed by lameness which kept him laid up twice as long. On February 15, 1731, he informed Aaron Hill: "Ever since I returned home, I have been in roaring pain with a violent rheumatism in my left shoulder." By March 14 he had recovered.

*Insomnia.*—He suffered from insomnia to which his frequent coffee imbibing contributed. He told Mr. Richardson in 1733: "I sleep in company and wake at night which is vexatious.

UNIVERSITY OF MICHIGAN LIBRARIES

As to my health it will never mend." He even nodded at the dinner table when he was entertaining Frederick, Prince of Wales.

*Eye affection.*—To add to the poet's troubles off and on he suffered from "weakness of the eyes". In 1721 he wrote to Lady Mary Wortley Montagu: "My eyesight is grown so bad that I have left off all correspondence save with yourself." Cheselden's advice seems to have been helpful to the poet. In his *Imitations of Horace* (*Epistle I To Lord Bolingbroke*) he writes:

> "Weak tho' I am of limb and short of sight,
> Far from a Lynx, and not a Giant quite;
> I'll do what Mead and Cheselden advise,
> To keep these limbs and to preserve these eyes."

In his letters to Warburton he several times alludes to increasing loss of vision. Thus in 1742 he writes: "My eyesight grows every day shorter and dimmer", and again in 1743: "Forgive my scribbling so hastily and so ill. My eyes are at least as bad as my head."

Pope suffered from myopia (short sight) from childhood, aggravated by eye strain through constant reading and writing. The myopia seems to have been slowly progressive and in later life was probably complicated by some eye affection which permanently damaged the poet's vision.

*Injury to hand.*—In November 1726, Pope had been dining with Bolingbroke at Dawley, and late at night the peer sent his friend home in a coach-and-six. A small bridge about a mile from Pope's villa was broken down, the coach went into the trunk of a tree and was overturned into the water. The water rose in the coach up to the occupant's periwig and the glass windows being up, Pope was in danger of drowning. The postilion, fortunately, came to his rescue and by breaking a window extricated him from the coach. In doing so, one of the pieces of glass severed the tendons of two of the fingers of Pope's right hand. This prevented him from writing for some time. He was treated for the injury by Nathaniel St. André, a skilful surgeon, but stiffness of the two fingers was permanent. St. André was the surgeon who was deceived by Mary Toft of Godalming who pretended to give birth to rabbits. Voltaire, who was staying with Bolingbroke at the time of Pope's accident, sent his condolences in a letter in English, stating that the water into which Pope fell was "not Hippocrene's water, otherwise it would have respected him." "Is it possible", he added, "that those fingers which have written the 'Rape of the Lock' and the 'Criticism', which have dressed Homer so becomingly in an English coat, should have been so barbarously treated?"

## Last Years and Death

As we have noted, the leading physicians and surgeons of the time were friends of Pope, and he frequently consulted them about his health. In a letter to Richardson (November 21, 1733) he relates that he has been to town for half a day "upon business with Dr. Mead and returned to render an account of it". Above all, he owed much to the constant medical care of his literary collaborator, Dr. Arbuthnot, and acknowledges it in the *Epistle* to him in these lines:

> "Friend to my life (which did not you prolong,
> The world had wanted many an idle song)."

In January 1739 Pope told Mr. Allen that he had been severely handled by his asthma. This may have been cardiac in origin, for by 1744 Pope also had ascites and œdema of the legs, signs of cardiac failure. He seems to have aggravated his symptoms by putting himself for a time in the hands of "a Dr. Thomson", a notorious quack. He still wrote, and was always saying something kindly about his friends. The old asperity and pettiness were gone.

With the advent of spring his mind was beginning to wander. At times he saw visions and was delirious. Once he imagined an arm was coming out of the wall of his room. A priest was summoned and Pope received the last rites with fervour and resignation. Next day, on May 30, 1744, he died peacefully at Twickenham in the presence of one or two friends. The heroic struggle of Alexander Pope's life against constant ills was over, and the victories he won in it are represented by his poetry which has secured for him an unchallenged place in English literature.

## References


Johnson, S. (1854) Lives of the British Poets. Alexander Pope, III, pp. 165–246, London.

The Works of Alexander Pope (1871–89) Edited by W. Elwin and W. J. Courthope with *Life* by W. J. Courthope in Vol. X; 10 vols. London.

Spence, J. (1820—2nd ed. 1858) Anecdotes, London.

Stephen, L. (1914) Alexander Pope. English Men of Letters Series, London.

Thackeray, W. M. (1885) The English Humourists of the Eighteenth Century. Collected Edition, XXIII, London.

Wharton, J. (1890) Life and Letters of Alexander Pope. London.

# John Arbuthnot, M.D., F.R.C.P., 1667–1735

By W. R. LeFanu, M.A.

*Librarian, Royal College of Surgeons of England*

JOHN ARBUTHNOT, mathematician, satirist, wit, and physician to Queen Anne, preserved many letters written to him by the distinguished men and women of his day. These letters were bought by Dr. William Hunter, bequeathed to Dr. Matthew Baillie, and given by Baillie's grandson to the Royal College of Surgeons of England. Some were printed in Aitken's *Life of Arbuthnot* (1892) and others in the Correspondence of Swift (1910–14) and Pope (1956). The purpose of this paper is to describe all these autographs.

Arbuthnot was born in Scotland in 1667. His father, a Jacobite episcopalian clergyman, was ejected at the Revolution of 1688, whereupon John came to London and taught mathematics. He graduated M.D. at St. Andrews in 1696, practised in London, and was elected F.R.S. 1704 and F.R.C.P. 1710. He had published three mathematical works, an exposure of William Woodward's theory of fossils, and a pamphlet in favour of the Union of England and Scotland.

He was appointed physician-in-ordinary to the Queen in 1709, and came into close friendship with her leading courtiers and ministers. He supported the peace policy of Lord Oxford's Tory government by his brilliant pamphlets "The History of John Bull". The collection of autograph letters shows that he was a friend of Lord Oxford himself, Lord Peterborough the distinguished general and diplomat, Lord Mar the Secretary for Scotland, the Duke of Montrose who kept Scotland loyal when Lord Mar led the Jacobite rising in 1715, the Duke of Shrewsbury, ambassador in Paris, and his Duchess, and the Mistress of the Robes, the Duchess of Somerset. He also became an intimate friend of the Tory writers, Swift and Pope and their companions Parnell and Gay; together they formed the Scriblerus Club, in which the "Prime Minister", Lord Oxford, also joined, and planned a combined satire on pedantry.



FIG. 1.—John Arbuthnot, M.D.

From the painting by Charles Jervas. By permission of the Royal College of Physicians.

Oxford fell from power on Tuesday, July 27, 1714, before the rivalry of his colleague Bolingbroke; but the Queen was dying. Arbuthnot was in attendance on her through a week of great uncertainty: was the Protestant succession to be secured in Prince George of Hanover, or would the Jacobites rise and bring in the Catholic Pretender, Prince James? On Sunday morning, August 1, she died. Tories suspected of Jacobite intrigue went in danger of arrest. Oxford was forbidden the Court, and Bolingbroke, who should have been Prime Minister, was attainted and fled to France. Swift retired to Ireland and did not see London again for twelve years. Francis Atterbury, Bishop of Rochester, who also was a friend of Arbuthnot, at first accepted the Hanoverian settlement, but a few years later was exiled. Another close friend was the painter Charles Jervas, but he is not represented by a letter here. His splendid portrait of Arbuthnot belongs to the Royal College of Physicians (Fig. 1).

The sole medical letter is from Boerhaave, advising treatment for Lord Berkeley, commander-in-chief of the Navy. Arbuthnot's own medical writings comprise two books—on *Aliments* (1731) and on the *Effects of Air* (1733). His Harveian Oration of 1728 made a plea for preventive medicine, including inoculation against small-pox. This had been lately introduced from the East by Lady Mary Wortley Montagu, but her surviving letters to Arbuthnot are on literary questions.

The Scriblerus satire came to achievement in 1726–28 in three masterpieces: Swift's *Gulliver*, Gay's *Beggar's Opera*, and Pope's *Dunciad*. Arbuthnot's contribution "The Scriblerus Memoirs" was included in Pope's *Miscellanies*, while his daughter Nancy

UNIVERSITY OF MICHIGAN LIBRARIES

Arbuthnot chose the music for the *Beggar's Opera*. From the last years of Arbuthnot's life there are four entertaining letters from the famous Lord Chesterfield, one very interesting letter from Swift describing his life in Dublin, and several charming letters from Pope.

Arbuthnot died on February 27, 1735; Pope and Chesterfield were with him the evening before, and Swift wrote that his death was "a terrible wound near my heart". The collection of letters concludes with Pope's heartfelt condolence to his son George Arbuthnot, and other letters that passed between them.

## CALENDAR OF LETTERS ADDRESSED TO JOHN ARBUTHNOT

WITH A FEW OTHERWISE ADDRESSED

3 July, 1704. Queen Anne. Order in Council with the Queen's sign manual, countersigned by Lord Treasurer Godolphin, for supplies for Lord Galway's Spanish campaign.

28 June, 1706. Charles Mordaunt, 3rd Earl of Peterborough, from the Spanish campaign, on politics and personal affairs.

2 August, 1712. John Erskine, 11th Earl of Mar, Secretary for Scotland, on his "aversness" to going to Scotland on an official visit.

18 September, 1712. Robert Harley, 1st Earl of Oxford, Lord Treasurer, thanking for news of the Queen's health.

23 March, 1713. Charles Talbot, Duke of Shrewsbury, ambassador in Paris, on the Queen's health; mentions Arbuthnot's brother Robert, a Jacobite banker in Paris.

14 April, 1713. Adelhida, Duchess of Shrewsbury, from Paris, asking for news from Court; mentions Dr. Helvetius. Postscript by the Duke, thanking for a letter.

8 August, 1713. James Graham, Duke of Montrose, Lord President of Scotland, asking Arbuthnot's influence for David Graham, a naval surgeon.

[December, 1713] Lord Oxford, on the Queen's illness.

[December, 1713] Elizabeth, Duchess of Somerset (Lady Elizabeth Percy, heiress of the Earls of Northumberland), Mistress of the Robes, apologizes for delay in returning to Windsor during the Queen's illness.

2 June, 1714. Jonathan Swift, Dean of St. Patrick's, to John Gay, advising him on his appointment as secretary to the embassy to Hanover.

16 June, 1714. Swift. On his life in the country and the impending fall of the Ministry.

11 July, 1714. Alexander Pope. On the Scriblerus Club, and a visit to Swift at Letcombe.

22 July, 1714. Swift, on the quarrel between Lords Oxford and Bolingbroke.

25 July, 1714. Swift. His visit to Oxford; his admiration for Arbuthnot; Pope's visit to him.

2 September, 1714. Thomas Parnell and Alexander Pope. On the Scriblerus Club; Swift's sudden departure for Ireland; Pope's "Homer" nearly completed.

12 July, 1721. Francis Atterbury, Bishop of Rochester, mentions a manuscript treatise, and invites Arbuthnot and Pope to visit him.

30 October, 1725. Hermann Boerhaave, Professor of Medicine at Leyden. A Latin consultation on the case of Admiral Lord Berkeley.

17 October, 1729. Lady Mary Wortley Montagu, asking Arbuthnot's intervention in an attack on her by Pope.

[October, 1729] The same, thanking for his intervention.

23 March, 1731. Philip Dormer Stanhope, 4th Earl of Chesterfield, British Minister at The Hague, discusses criticism of him by an unknown lady; promises the success of his mission [to arrange the marriage of the Princess Royal with the Prince of Orange].

6 April, 1731. The same, on politics and personal affairs.

20 April, 1731. The same, requiring Arbuthnot's "attention and skill" for his mind and body.

29 June, 1731. The same, on Arbuthnot's losses at cards; court gossip.

12 June, 1734. Henry St.John, Viscount Bolingbroke, on the affairs of M. de Chavigny and Robert Arbuthnot; John Arbuthnot's failing health.

15 July, 1734. Pope. A visit to Lord Bathurst; Arbuthnot's health.

25 August, 1734. The same. A visit to Lord Peterborough; personal.

3 September, 1734. The same. Personal.

[November, 1734] Swift. A long description of his way of life in Ireland.

[3 January, 1735] Lady Mary Wortley Montagu, refuting Pope's attack on her in his newly published *Epistle to Dr. Arbuthnot*.

1 March, 1735. Pope to George Arbuthnot, in condolence on his father's death.

29 October, 1741. Pope to the same. Refusal to reprint John Arbuthnot's "Sermon at Edinburgh"; invites Nancy Arbuthnot to Bath.

[February, 1742] George Arbuthnot to Pope. Appointment with Lintot the publisher; with a note added by Pope.

23 July, 1743. Pope to George Arbuthnot, on their plan to stay together at Bath.

## REFERENCES

AITKEN, G. A. (1892) The Life and Works of John Arbuthnot. Oxford.

POPE, A. (1956) Correspondence, edited by G. Sherburn. Oxford. 5 volumes.

SWIFT, J. (1910–14) Correspondence, edited by F. Elrington Ball. London. 6 volumes.

# Section of Neurology

President—W. RITCHIE RUSSELL, C.B.E., M.D., D.Sc., F.R.C.P.

[*February* 6, 1958]

## DISCUSSION ON SURGERY OF TEMPORAL LOBE EPILEPSY

**Mr. D. W. C. Northfield** (London):

I would like first to examine the significance of the term "temporal lobe epilepsy". If the term is accepted without qualification or reserve, we are linking a particular anatomical region with a symptom-complex. Its validity then rests upon two theses; that disturbance of function within this area will give rise to the peculiar phenomena which we call epilepsy, and the concept of the "epileptic focus". In support of the validity is operative experience, that in about half the cases the result is successful. This applies also for operations elsewhere in the brain for the relief of epilepsy. In successful and uncomplicated cases, amputation of one temporal lobe rarely results in loss of intellectual or other function of a measurable degree, except for hemianopia of greater or lesser extent. This seems surprising, in view of the great variety of epileptic patterns these patients may display, if these patterns are evoked exclusively within the affected temporal lobe. The results which Penfield (Penfield and Rasmussen, 1950) obtained by stimulating various areas of the temporal lobe, evoking memory patterns, perceptual illusions and hallucinations, were obtained only in patients with epilepsy; as Penfield puts it, it is as though the repeated epileptic discharge had conditioned the brain to react in this way. But it would be rash to assume from these experiments and from the successful results of lobectomies that this portion of brain functions as a storage area for memory or serves a specific function in organizing perception. Perhaps only in the hallucinations of smell, hearing, vision and equilibrium and in the arrest of speech during a fit are we seeing disturbance of function restricted to the temporal lobe. In a correlation of the site of the lesion with the seizure pattern, Penfield and Kristiansen (1951) found that in 13 cases of perceptual illusion the lesion was frontal in 4 and temporal in the others; fear occurred in 2 cases of temporal lesion and 1 of frontal; automatism occurred in 2 frontal lesions and 17 temporal. Although the use of cases of tumour is open to criticism, the evidence should not be entirely disregarded. In a recent analysis, Atkinson (1957) found in 69 cases of frontal tumour that there were 24 in which olfactory, auditory, vestibular, visceral and psychical seizures occurred. In 63 cases of temporal lobe tumour these patterns occurred in 57. Indeed there is much evidence that forms of epilepsy which we associate with temporal lobe disorder can arise from lesions outside the temporal lobe, but little evidence that these highly complicated seizures are exclusively disturbances of temporal lobe function. It may well be that an epileptic discharge in the temporal lobe produces its remarkable phenomena by discharging through the hippocampus and its connexions to central areas of the brain thence to be widely dispersed. Indeed, the discharge may originate in the temporal portion of the limbic lobe. This, of course, is a hypothesis which has already been frequently put forward and offers a more acceptable explanation for the seizures. The term "temporal lobe epilepsy" is widely used and is harmless only so long as it merely implies the suspected anatomical situation of a so-called epileptic focus; it should not tempt us to label that area of brain with certain functions.

The validity of the concept "temporal lobe epilepsy" depends also upon that of the notion of the "epileptic focus". Surgery of epilepsy has been based upon the assumption that in a particular area neurones are so disturbed in their function that they periodically discharge in a manner which may spread locally through the cortex, to stimulate neighbouring neurones, or by discharging along pathways may excite neuronal activity at a distance, and perhaps widely dispersed. By removing this focus, the condition should be cured. In electroencephalography, a mass of observational data has been built up which gives assistance to the surgeon in so far as it provides confirmation of the presence and the locality of such a focus before operation, and delimits the abnormality during the operation. The use of cortical stimulation to evoke a typical seizure in the conscious patient seemed to provide additional support for the concept of the epilepsy focus. But the use of newer techniques in electroencephalograpny and the more thorough study of individual cases are beginning to cast doubts upon this hypothesis. Records may demonstrate the continued presence of those abnormalities over one temporal lobe which are considered typical of the epileptic focus, but abnormalities may also be recorded from other parts of the scalp at the same or at other sessions. This is particularly so for the other temporal area and such abnormalities may not be synchronous; difficulty often arises in deciding which is the more abnormal side. Abnormal records may be obtained from areas other than the temporal. Similarly, electrocorticography may more accurately reveal abnormalities arising in other parts of the



UNIVERSITY OF MICHIGAN LIBRARIES

brain and these abnormal discharges are perhaps more particularly to be found in the orbital surface of the frontal lobe. It is difficult to reconcile the concept of a "focus" with the experience at operation when spike discharges appear in cortex beyond the lobectomy, in areas where earlier there had been none. Russell Myers (1954) has drawn attention to the presence of spike discharge in the thalamus and in the caudate nucleus recorded by electrodes implanted in those structures in cases of temporal lobe epilepsy. The spikes in the deep structures were sometimes independent of and sometimes related in time to those from the temporal cortex. Faeth *et al.* (1954) have studied the manner of spread of experimental epileptic discharge excited in the cortex of animals and have found that it follows certain preferential pathways to other cortical areas and to deep structures, according to its area of origin. Whether the continued bombardment of deep or distant neurones eventually leaves them in a potentially epileptic state is as yet unknown, but recently acquired knowledge of the physiology of the nerve cell (Eccles, 1953, 1957) allows one to entertain this possibility. Although seizures in a particular patient may not be frequent, one must bear in mind that, judging by repeated interseizure EEG records, the brief and high potential changes which we call spikes are occurring at random intervals many times a minute throughout the twenty-four hours. Their cumulative effect may be out of all proportion to the number of clinical seizures. It may well be, therefore, that the time-honoured concept of an epileptic focus must be modified so as to envisage in every case the presence of abnormal cells in more distant structures. Such modification does not deny the value of operation; indeed, this would run counter to the successes secured. In these, one might accept the explanation that the area of brain removed included a constellation of the most unstable cells. The failures might be explained by an inadequate resection, or by the undetected domination of the deep or distant cell groups.

The term "temporal lobe epilepsy" has its uses in concentrating attention upon a particular portion of brain, and its simplicity is attractive. But as a catch-phrase it glosses over the obscurities in this fascinating field of study, and may easily put one in blinkers. For myself, I prefer the broader and less committing term "psychomotor epilepsy" against which, however, plenty of criticism can also be levelled.

It is unnecessary to emphasize here the importance of an accurate account of the fits, in order to make a clinical or symptomatic classification of the disorder; likewise the need for a thorough physical examination. By such means we are enabled to judge the need for and the choice and the direction of more elaborate investigations. The clinical picture may indicate the likelihood of a tumour, a vascular abnormality or a diffuse brain disease. On the other hand, it may reveal the extent of dependence upon thorough EEG recording. Although several scalp recordings may give reassuring and apparently convincing evidence of the presence of a focal electrical abnormality in one temporal area, the aim and the ultimate value of the electroencephalographer should be to provide information of the presence and the dominance or otherwise, of the distant or deeply linked epileptic areas. In this field the development of special EEG techniques has been remarkably hesitant. The use of sphenoidal leads has given valuable information concerning activity from the under-surface of the temporal lobe and the use of two sphenoidal leads on each side has been a useful elaboration. But the information which might be of the greatest assistance in solving our problems lies deeper. Accurately localized and more detailed abnormalities can be detected by the use of electrodes inserted into the subdural space over appropriate areas of the cortex and with these, serial electrocorticographic records can be obtained over periods of days. They sometimes clarify the obscurities of scalp recordings and may shift attention from the temporal to the frontal cortex. The detection of abnormalities in the basal ganglia can be attempted by the insertion into them of leashes of fine wire electrodes. Information by these methods is at present scanty but it is a field of enquiry urgently needing investigation. Implantation of electrodes in my small experience has carried surprisingly little risk so far and such risk may be justifiably accepted in selected patients. Without prospect of relief, they may be condemned to a life in an institution or to suffer permanently under a severe social and economic handicap. If such a patient were found to have a tumour the much greater risk of its removal would be readily accepted. Finally, the full exploitation of the EEG during operation has not yet been achieved. We have the example of Penfield's many years of careful observations on cortical stimulation. A similarly thorough application of the techniques of the EEG may well bring dividends, not only in controlling the extent of the brain resection, but as a programme of research into the mechanism of epilepsy.

In conclusion, I would like briefly to recount our experiences at the London Hospital with which my colleague Mr. J. V. Crawford has been associated, and where we are much indebted to Dr. S. L. Last and his staff for their enthusiastic and tireless help. I was uncertain what cases to review, for epilepsy is, of course, encountered in many cases of tumour of the temporal lobe and I decided to exclude all tumour cases, but I have included two cases of angiomatous malformation. The indication for operation therefore was epilepsy,

resistant to drugs, and causing severe social and economic disabilities. Some patients came from institutions for the care of epileptics, some from mental hospitals where they were voluntary or certified inmates and the remainder from general hospital practice. This series comprises 31 patients; one patient died of a pulmonary embolus and the analysis is concerned with the remaining 30 (Table I). The cases are separated into three groups

TABLE I.—RESULTS REGARDING EPILEPSY

| Good | | | Fair | | | Unimproved | | |
|---|---|---|---|---|---|---|---|---|
| | Length of history (years) | | | Length of history (years) | | | Length of history (years) | |
| Patient | Pre-op. | Post-op. | Patient | Pre-op. | Post-op. | Patient | Pre-op. | Post-op. |
| M. G. | 10 | 5 | J. H. | 17 | 4 | M. B. | 36 | 4¼ |
| D. J. | ½ | 4 (?0) | D. P. | 2½ | 3½ | M. P. | 5 | 4¼ |
| T. L. | 10 | 4 | P. M. | 2 | 3 (X) | H. M. | 22 | 4 |
| H. R. | 5 | 4 | B. L. | 2 | 3 | J. B. | 10 | 3¾ |
| W. M. | 8 | 3½ (0) | K. F. | 1 | 2¼ | L. S. | 9 | 3 |
| R. T. | 13 | 3½ | N. L. | 12 | ½ | P. R. | 9 | 3 |
| G. W. | 27 | 3 | | | | H. G. | 7 | 2 (X) |
| I. F. | 14 | 2 (0) | | | | G. S. | 17 | 2 (X) |
| G. T. | 26 | 1½ (?0) | Only 2 working | | | P. C. | 8 | 1½ (X) |
| M. M. | 5 | ¾ (0) | | | | I. B. | 24 | 1 |
| J. H. | 14 | ½ (0) | | | | P. G. | 15 | 1 (X) |
| V. M. | 10 | ¼ (0) | | | | I. W. | 12 | ½ |
| All working except J. H. | | | | | | Only 4 working | | |

Employment: 7 are working now—who were not before operation.
1 was working before, who has not yet returned.
(0)—no fits since operation.
(X)—craniotomy and electrocorticography, but no lobectomy.

according to the effect of the operation upon the epilepsy, and they are arranged in the order of time since the operation. It will be seen that in 5 cases, although craniotomy was carried out, no brain was resected because the electrocorticographic record led us to believe that lobectomy would be useless. Having reviewed these cases in the light of greater experience, I think this may have been a wrong decision and now I probably should have resected brain in one or two of these patients. The criteria adopted for classifying the result are arbitrary and open to criticism, except for the group of unimproved! The result has been deemed good if the seizures have been dramatically reduced, to say one or two a year, or where there have been only a few immediately after operation and then periods of freedom for a year or so. A fair result is one intermediate between good and no improvement, there being a substantial reduction in the number of fits. Anticonvulsants have been continued after the operation in nearly every case. Operation has provided a net gain to employment of 6 patients. It is worthy of comment that neither a long history of fits nor a family history of fits precluded operation. In the group of 12 good results, over half the patients had had fits for ten or more years and in 2, for twenty-six and twenty-seven years respectively. A family history of epilepsy was obtained in 6 patients and in 4 of these the result has been good.

There were 16 patients who exhibited mental symptoms of varying degrees (Table II).

TABLE II.—RESULTS REGARDING MENTAL SYMPTOMS

The common disorder was aggressiveness, with or without overt violence. A few patients were withdrawn, intellectually backward, paranoid. 11 were in mental hospitals prior to operation.

*Good in 8:*
5 were in mental hospitals.
Before operation, 2 were employed.
Since operation, 6 are employed (4 of these were in mental hospitals).
Epilepsy result: good 4, fair 3, unimproved 1.

*Fair in 2:*
Both were aggressive. 1 is described as "boisterous", but not aggressive. In the other aggression is replaced by mild dementia.
Both unemployed before and since operation.
Epilepsy result: fair 1, unimproved 1.

*Unimproved in 6:*
4 were in mental hospitals before operation, and remained there after operation.
Epilepsy result: fair 2, unimproved 3, 1 liable to temper tantrums, has returned to ordinary school but operation too recent to assess: no epilepsy as yet.

In one-half of these, there has been a great improvement and a gain to employment of 4. It will be seen that the effects of operation upon behaviour disorder are loosely related to its effects upon epilepsy, but in this small series no further conclusions can be

UNIVERSITY OF MICHIGAN LIBRARIES

drawn. The experience derived from individual cases makes it clear that behaviour may be much improved yet the fits may persist. The 2 patients in this series who have had a frankly schizophrenic type of illness have remained so. Two patients (M. G. and H. R.) previously reported (Liddell and Northfield, 1954), formerly certified as mental defectives, continue to be classified as a good result regarding both epilepsy and behaviour and they are earning their living five and four years respectively after operation.

The results of operations for epilepsy do not on paper make a very impressive showing whatever part of the brain may be affected. And when one considers the many hours of industry given to these patients both before and during the operation, one is tempted to regard the return as inadequate; but if operations for malignant disease were as successful we should be very gratified. Though the life of these patients may not be in danger, the psychological, social and economic effects of epilepsy can exert a continuing malignant influence upon the patient's whole existence. The results of operations for epilepsy should be viewed against that background and our dissatisfaction should serve as a spur to efforts to solve the problems provided by our failures.

## REFERENCES


ATKINSON, W. J. (1957) Thesis, M.S. London.

ECCLES, J. C. (1953) The Neurophysiological Basis of Mind. Oxford.

—— (1957) The Physiology of Nerve Cells. Baltimore.

FAETH, W. H., WALKER, A. E., and ANDY, O. J. (1954) *Epilepsia*, 3rd ser., **3**, 37.

LIDDELL, D. W., and NORTHFIELD, D. W. C. (1954) *J. Neurol. Psychiat.*, **17**, 267.

MYERS, R. (1954) *Epilepsia*, 3rd ser., **3**, 9.

PENFIELD, W. H., and KRISTIANSEN, K. (1951) Epileptic Seizure Pattterns. Springfield, Ill.

——, and RASMUSSEN, T. (1950) The Cerebral Cortex of Man. New York.


**Dr. Denis Hill** (London): *Indications and Contra-indications to Temporal Lobectomy*

The surgical work of Wilder Penfield and his colleagues at Montreal, carried out during the ten years 1939 to 1949, was a great stimulus to many who were concerned with the treatment of epilepsy. The first report concerned with temporal lobe epilepsy was made in 1950 by Penfield and Flanigin and it was some disappointment to us that patients with gross personality or mental disorder were largely excluded from their series. My colleagues and I had since 1944 (Hill, 1944, 1952; Rey *et al.*, 1949) recognized by the EEG method abnormal function in the temporal areas in some non-epileptic persons who suffered from such disorders, and reported our findings in a series of studies. Our hope was that the work of Penfield on the one hand, and of F. A. Gibbs *et al.* (1947) in relation to psychomotor epilepsy on the other, might provide the links which would lead to a better understanding and possible treatment not only of some epileptics but also of some psychopathic persons. Only part of this anticipation has been realized.

The creation of the Guy's-Maudsley Neurosurgical Unit and the active interest and collaboration of Mr. Murray Falconer, who has performed all our temporal lobectomies, provided an opportunity to test these ideas. The first operation was performed in March 1951 and we have reported results at intervals—the first 14 cases in 1953 (Hill *et al.*, 1953), 31 cases in 1955 (Falconer *et al.*, 1955) and last year at a meeting in the United States a follow-up study on 50 patients. At the present time about 75 have been submitted to surgery. During this period of seven years we have collected data on these patients from a number of points of view—clinical, electroencephalographic, radiological, psychological, pathological—and have related these to the results of the operations obtained from the follow-up study. As a consequence our ideas about the indications and contra-indications for this operation have undergone repeated changes.

The patients I am considering are those who have been referred to the epileptic outpatient clinic and have been admitted to a small unit in the Maudsley Hospital for the study of epileptics with psychiatric symptoms. There is therefore a complete selection of patients of this type. After study, usually lasting two to three months, a proportion have been referred to Mr. Falconer for consideration for surgery. These have contributed a proportion, and a varying one each year, of the total number of patients submitted to temporal lobectomy, since such patients are also referred from other sources. Many such patients naturally come from Guy's Hospital, and on the whole these are less ill from the psychiatric point of view than those studied in the Maudsley Unit. It is generally believed that about 50% of patients with temporal lobe epilepsy have abnormal personalities and that about 25% suffer psychotic episodes. All those which we have studied fall into this category.

During the last four years Dr. Desmond Pond and I have studied in hospital 144 patients in whom the diagnosis of temporal lobe epilepsy has been established in our belief. While the diagnosis in outpatients was often in doubt, and routine EEG investigations negative, we were able to find on repeated study as inpatients, spike foci in the EEG in 139 patients. In only 5 patients were we unable to find such foci, yet the diagnosis on clinical grounds

seemed irrefutable. It is useful to consider the practice of the last four years year by year, since the number of cases is approximately the same each year, and during this time the accumulated data on the results of the previous years was available in sufficient numbers to provide prognostic factors. Of these 144 patients, 33 (or 23%) were recommended for surgery, but the proportion has fallen from 36% in 1954 to 7% in 1957 (Table I).

TABLE I.—CASES OF TEMPORAL LOBE EPILEPSY

| | 1954 | 1955 | 1956 | 1957 | Total |
|---|---|---|---|---|---|
| Cases investigated .. .. | 36 | 31 | 36 | 41 | 144 |
| Recommended for surgery .. | 13 | 11 | 6 | 3 | 33 |
| | (36%) | (35%) | (17%) | (7%) | (23%) |

This decrease in those recommended for surgery from over a third in 1954 to less than 1 in 10 in 1957 for these very mentally abnormal groups of epileptics, has been due to the impact on us of a number of observations. Firstly, the real disability in the majority of these patients arises from their abnormal personalities, and we have little reason to believe that temporal lobectomy is of any help to them if their fits are controlled or very infrequent yet their mental abnormalities persist. Psychological disorder alone, in the absence of continuing fits, is not in our view an indication for surgery. Next, we had observed that patients with EEG spike foci in areas other than those recorded from the sphenoidal electrodes did not do well after surgery. In practice this usually meant that we had elicited multiple EEG foci—that is, not only a spike focus at one or both sphenoidal electrodes, but also similar and independent foci at the mid-temporal or posterior temporal electrodes on the scalp or in the frontal areas. This led from its observation in 1955 to much more intensive and prolonged EEG study. At the same time came the observation of our colleagues Meyer and Yates (1955) that operations on the left temporal lobe in right-handed patients may endanger their subsequent capacity to remember what they had heard. This auditory learning deficit can be on occasion a serious disability in patients whose occupation entails the immediate recall of auditory perceptions, as is the case with telephone operators, for example. We have therefore been reluctant to recommend the operation to patients of average or above average intelligence who have temporal lobe epilepsy of the dominant hemisphere. From the personality aspect we had also observed that while those patients with overtly aggressive tendencies did well after surgery, those with inadequate or hysterical personalities did poorly, as did also those suffering from chronic paranoid psychoses. Evidence of generalized cortical atrophy or grossly dilated or asymmetrical ventricles, seen in the AEG, was also regarded as a contra-indication, although only found in 6 of the 144 cases (Table II).

TABLE II.—GROUNDS FOR CONSERVATIVE TREATMENT

| No. investigated | 1954 (36) | 1955 (31) | 1956 (36) | 1957 (41) | Totals (144) |
|---|---|---|---|---|---|
| Fits controlled .. .. | 6 | 13 | 15 | 24 | 58 (40%) |
| Multiple EEG. foci .. | 7 | 3 | 8 | 8 | 26 (18%) |
| Personality .. .. .. | 2 | 2 | 3 | 3 | 10 (7%) |
| Other factors* .. .. | 8 | 2 | 4 | 3 | 17 (12%) |
| >2 factors .. .. .. | 6 | 6 | 16 | 16 | 44 (31%) |

*e.g. AEG (6), no focus (5), miscellaneous (6).

Our experience has led us to believe that when temporal lobectomy is successful in bringing about a control of seizures, it is also nearly as successful in causing an improvement in the personality disorder. It is therefore, we believe, the treatment of choice if the seizures cannot be controlled by drugs. Complete control or rare seizures are, however, an absolute contra-indication. As Table II shows in 40% of the 144 patients, the fits were adequately controlled by anticonvulsants. The number so controlled has increased from 16% in 1954 to over 58% in 1957. This is possibly due to the more energetic use of anticonvulsants, in turn due to the fact that a number of other factors, in some degree adverse to surgery, but in themselves not considered an absolute bar, were present. Thus while 38% showed hysterical or inadequate personalities, the personality grounds were the main reason for conservative treatment in only 7% of the 144 cases. Again while 35% showed multiple EEG foci, this was the main reason for conservative treatment in only 18% of the total. Taking into account these multiple factors, each of them in some degree adverse to a good surgical prognosis, it is seen that the number of patients showing more than two such factors was 31% of the total, and that the proportion of such cases has almost trebled in the last two years.

In our endeavours to find the factors or group of factors which, if present, lead to a clear indication for surgery and by contrast those factors which carry an unfavourable prognosis, we have perhaps been over-zealous in our investigatory enthusiasm. This is illustrated by the EEG studies. The more intensively these are pursued the greater the probability that multiple foci will be found (Table III).

UNIVERSITY OF MICHIGAN LIBRARIES

TABLE III.—MULTIPLE EEG FOCI

| Type | 1954–5 (67 cases) | 1956–7 (77 cases) |
|---|---|---|
| Bilateral sphenoidal, no lateralization | 8 | 12 |
| Sphenoidal + other spike focus .. | 7 | 24 |
| >2 foci .. .. .. .. | 8 | 22 |
| >3 foci .. .. .. .. | 1 | 10 |

It would seem to us that less than 1 in 10 of this severely abnormal group of temporal lobe epileptics are suitable for surgery. It is necessary to emphasize that these patients are probably the most seriously disturbed of all epileptic patients. In them adverse social and environmental, genetic and organic, factors are found together. It has surprised us that the energetic exhibition of anticonvulsants has resulted in such good results as regards fit control—over 58% being rendered almost fit-free in the last year, and 40% for the four years summed together. Comparable psychological improvement has not, of course, occurred but some improvement there has been. It will be necessary now to make a follow-up study of this group treated conservatively yet energetically by drugs. No doubt many of these patients will later become decontrolled and some will be subjected to surgery.

*Indications for Surgery*

The demonstration of a strictly unilateral spike focus in the EEG recorded at the sphenoidal electrode, or in the case of bilateral temporal spike foci, the clear demonstration that one side is constantly predominant and most active, has been hitherto the essential criterion for surgery. Failure to demonstrate dominance between bilateral foci, or the presence of additional foci elsewhere, has been regarded as a contra-indication. The EEG data, together with the failure to control seizures by drugs, have been the most important indications. In doubtful cases, the attempt to determine the site of origin for the seizure by the use of activating drugs, such as Metrazol or Megimide, has not proved helpful in our hands, since on different occasions different sites of origin have been found in the same patient. Unless the habitual aura and type of seizure pattern is produced by the procedure, uncertainty as to the significance of the activation remains. We cannot therefore as yet place much reliance on these methods.

At the present time the most useful EEG indication, apart from the spike focus, is one which has come from a correlation study between the pre-operative EEG data and the histological data obtained from the biopsy specimens. Our colleagues Cavanagh and Meyer (1956) have divided the biopsy material into two main groups. The first are those with focal macroscopic lesions, mostly very small tumours, and the second are those with diffuse atrophic lesions. This second group can be subdivided into those with gross Ammon's horn sclerosis and those without this lesion. In the follow-up study it is clear that the first group, those with small tumours, do very well after temporal lobectomy, while of the second group, those with Ammon's horn sclerosis obtain much greater relief from this operation than those in whom the lesions are disseminated. This group with Ammon's horn sclerosis in fact constitutes 40% of patients subjected to operation in our series, and their prediction pre-operatively is important, since for them the surgical prognosis is good (Table IV).

TABLE IV

| Ammon's horn sclerosis | No. | Relief from epilepsy + | Relief from epilepsy — | Improvement in personality + | Improvement in personality — | Improved working ability + | Improved working ability — |
|---|---|---|---|---|---|---|---|
| Present .. .. | 21 | 18* | 3 | 16† | 5 | 16 | 5 |
| Absent .. .. | 15 | 7 | 8 | 4 | 11 | 5 | 10 |

*Relief—fit free (12 cases) or 50% improved (6).
†Two pre-operative personalities normal.

A study carried out with Dr. W. A. Kennedy (1958) on the detailed pre-operative EEG data on 50 cases has shown that it is not possible to predict on EEG grounds alone the Group I cases, i.e. those with small tumours. However, in most of these patients the seizures start in adolescence or early adult life as opposed to childhood. We have, however, found a clear relationship between pathological involvement of the medial temporal lobe structures, which in practice means for the majority Ammon's horn sclerosis and one EEG character, obtained from the Pentothal narcosis records. (All our patients are investigated under Pentothal and all are examined with sphenoidal needle electrodes.) This EEG character is reduction or absence of the prominent barbiturate-induced fast rhythm recorded between the sphenoidal needle and the ear electrodes on the side of the lesion. This finding enables

one to predict Ammon's horn sclerosis or, in the case of tumour, gross pathological involvement of the medial structures of the temporal lobe with some confidence (a finding significant at the 1% level).

CONCLUSIONS.—The indications and contra-indications to temporal lobectomy cannot obviously be stated in a few words. Granted that a patient is suffering from temporal lobe epilepsy and that the seizures cannot be controlled by drugs, the issues regarding surgery have become complicated by our increasing knowledge about the electrical manifestations of the disorder, about its psychological aspects and about the surgical effects on psychological function which may follow. All these may have implications for future policy regarding the time when surgery should be pursued. It may be, for example, that surgery should be advised in some cases at an earlier stage in the development of the disorder. The evidence for this is not yet clear enough to guide policy. Although my colleagues and I have felt constrained in the last two years to adopt more conservative treatment for the majority of our patients, we are still convinced of the undoubted value of surgery in suitable cases. It must again be emphasized that we have been concerned with those patients with severe psychological disorder—the worst half of the temporal lobe epileptic population. In order to show our present ideas in clearer form, I have tabulated indications and contra-indications under three headings, including a group of factors which we believe are neutral and can be disregarded when the issues as to surgery are under consideration (Table V).

TABLE V

| | | |
|---|---|---|
| | | *Factors Favouring Surgery* |
| *EEG* | (1) | Reduced barbiturate-fast rhythm beneath temporal lobe. |
| | (2) | Unilateral sphenoidal spike focus. |
| | | (If bilateral, only at opposite sphenoidal electrode.) |
| *SIDE* | (3) | Non-dominant hemisphere. |
| | | (If dominant consider occupation.) |
| *PSYCHOL.* | (4) | *Personality:* normal or aggressive. |
| | (5) | *Concordance* of EEG, clinical, AEG and psychological data. |
| | | *Neutral Factors* |
| *EEG* | (1) | Infrequent contralateral sphenoidal focus. |
| | (2) | Occasional subcortical discharges. |
| | (3) | Symmetrical barbiturate-fast rhythm. |
| *AEG* | (4) | Slight asymmetry of temporal horns. |
| *PSYCHOL.* | (5) | I.Q. range above 60. |
| | (6) | Psychosis. |
| | | *Contra-indications* |
| *EEG* | (1) | Dominant spike focus *not* at sphenoidal electrode or ear. |
| | (2) | No clear dominance in multiple foci. |
| | (3) | Fast rhythm reduction predominantly outside temporal areas. |
| *AEG* | (4) | Cortical atrophy. Grossly dilated or asymmetrical ventricles. |
| *PSYCHOL.* | (5) | Hysterical or very inadequate personality. |
| | | Paranoid psychosis. |
| | | ? Dominant lobe in high I.Q. |
| | (6) | Conflict of data. |

The work described in this paper is the result of collaboration and it is a pleasure to acknowledge the help of Dr. Desmond Pond, Dr. W. A. Kennedy and Dr. Richard Hoare.

## REFERENCES

CAVANAGH, J. B., and MEYER, A. (1956) *Brit. med. J.*, ii, 1403.
FALCONER, M. A., HILL, D., MEYER, A., MITCHELL, W., and POND, D. A. (1955) *Lancet*, i, 827.
GIBBS, F. A., GIBBS, E. L., and FUSTER, B. (1947) *Trans. Amer. neurol. Ass.*, **72**, 180.
HILL, D. (1944) *Proc. R. Soc. Med.*, **37**, 317.
—— (1952) *Electroenceph. clin. Neurophysiol.*, **4**, 419.
——, FALCONER, M. A., and PAMPIGLIONE, G. (1953) *Proc. R. Soc. Med.*, **46**, 965.
KENNEDY, W. A., and HILL, D. (1958) *J. Neurol. Psychiat.*, **21**, 24.
MEYER, V., and YATES, A. J. (1955) *J. Neurol. Psychiat.*, **18**, 44.
PENFIELD, W., and FLANIGIN, H. (1950) *Arch. Neurol. Psychiat., Chicago*, **64**, 491.
REY, J. H., POND, D. A., and EVANS, C. C. (1949) *Proc. R. Soc. Med.*, **42**, 891.

**Mr. Murray A. Falconer** (London):

My part in this discussion is to consider the results of surgical treatment in temporal lobe epilepsy and the lessons which we have learnt from it. To Professor Wilder Penfield and his various colleagues at Montreal must go the chief credit for developing this field of surgery, but many other workers in different parts of the world have also made substantial

contributions. There is now fairly general agreement that in order to achieve the best results it is necessary to remove not only the superficial temporal convolutions of the anterior third or half of the temporal lobe, but also the deeper structures, including the anterior part of the hippocampal gyrus, the uncus, the amygdala and the hippocampus. Picaza and Guma (1956) of Cuba, who have recently reviewed the literature, have shown that highly successful results have been obtained at several centres in more than 50% of cases submitted to operation.

At the Guy's-Maudsley Neurosurgical Unit we have now performed an anterior temporal lobectomy for epilepsy in 75 cases, with only 1 death, the second patient in our series. As some of these cases have only recently been operated on, I propose to confine my remarks to the first 50 patients who have now been operated on and followed up for periods of from two to seven years. In all a large space-occupying lesion had been excluded by the pre-operative clinical and neuroradiological studies. Furthermore, in none was a circumscribed lesion visible at operation in the exposed brain, consequently each was submitted to a standardized block resection of the lobe. Certain aspects of these patients have already been reported (Cavanagh *et al.*, 1957; Falconer *et al.*, 1957; Falconer and Wilson, 1958; Kennedy and Hill, 1958).

In the *selection of patients for operation* we took into consideration two sets of factors:

(1) The occurrence of fits of psychomotor type which had proved intractable to drug therapy. The frequency of such attacks ranged from one to two per month to several in a day. In addition, major convulsive seizures had been observed in 25 of the 50 patients.

(2) The demonstration by electroencephalography of a spike-discharging focus which was situated predominantly in the anterior part of one temporal lobe. The technique of examination has been referred to by Dr. Hill, and has previously been described by Pampiglione and Kerridge (1956). Such a focus was demonstrated in 49 of the 50 patients, and the abnormality was confined to one side in 28 patients. In 21 patients there were also spike discharges in the opposite temporal lobe. Sometimes these contralateral discharges were very infrequent, but arbitrarily they were always less than 25% of the activity exhibited on the side to be operated. At the stage of our experience when we selected these patients we did not realize the special significance of diminished barbiturate-fast activity between the sphenoidal electrode and the ear electrode (Kennedy and Hill, 1958). In one of our patients the EEG was normal, but as the patient had dysphasia as an aura, we chose the left side for operation on the clinical localization, and subsequently the specimen revealed a small cortical infarct secondary to arteriosclerosis.

In 5 of our patients the pre-operative personality was judged to be normal, but in 45 there was an associated personality disturbance of varying severity. At the time of selection we did not then know how the various personality disorders would respond, and so we garnered a variety of disturbances of which sudden outbursts of aggressiveness were the most common (19 patients). Other types of personality disorder included continued aggression with paranoid features (7 patients), inadequate ineffectual personalities (5 patients), hysterical personalities (9 patients), and a miscellaneous group (5 patients). Transient psychotic episodes had occurred in 7 patients.

*General principles of operation.*—The operation has usually been performed under local analgesia with electrical stimulation of the exposed brain and monitoring of the electrical discharges by electrocorticography (Falconer *et al.*, 1955). In most neurosurgical centres the affected temporal lobe is removed by suction, thus precluding adequate histological examination of the resected tissue. In all our cases the anterior part of the temporal lobe (5 to 9 cm.) was resected in one piece, the specimen comprising the lateral and inferior temporal convolutions anterior to Labbé's vein, as well as the uncus, anterior hippocampus and amygdala. Such a resection was carried out whether or no electrocorticography showed spike discharges present in the posterior temporal or suprasylvian regions, for experience has shown us that provided the main discharging areas are situated anteriorly, particularly in the uncinate and amygdalar areas, a good result can be expected.

In our material the left temporal lobe was removed in 33 patients, the right in 16 patients, and both temporal lobes in one. The reason for this left sided predominance is not known. It is in keeping with the experience of most investigators in this field (Meyer and Jones, 1957), but not with all (Baldwin, 1958).

*Physiological effects of operation.*—Certain effects have been noted so frequently that they may be regarded as coincidental effects of removal of the temporal lobe:

(1) Some degree of homonymous hemianopia was present in every case. Generally it took the form of a congruous contralateral, upper quadrantic, homonymous hemianopia which was less than a quadrant. In 8 patients, however, the defect was greater than a quadrant. There was no constant relationship between the amount of temporal lobe removed and the degree of the hemianopia (Falconer and Wilson, 1958).

(2) A very slight but persistent degree of nominal aphasia was noted in 13 of the 33 patients in whom the dominant temporal lobe had been removed. The degree of disturbance was usually a difficulty in naming one or two out of ten common objects, and was seldom noted by the patient himself because of ready paraphrasing.

(3) A definite deficit of learning by auditory modalities, but without impairment of visual or kinæsthetic learning and without overall loss of intelligence has been observed in every patient in whom the dominant temporal lobe has been removed (Meyer and Yates, 1955; Meyer and Jones, 1957). Very few patients have noticed this deficit themselves or been handicapped by it, largely because they have learnt to compensate by using the other modalities. Thus businessmen have been able to carry on their work using paper and pencil to record verbal instructions. A telephonist, however, had to change his occupation. We have not yet observed the effect of removal of the dominant temporal lobe in a student attending one of the higher institutions of learning, but we imagine it might prove crippling.

*Pathological findings.*—The various temporal lobes, so removed *en bloc*, have subsequently been examined histologically by Professor A. Meyer and Dr. J. Cavanagh (Meyer *et al.*, 1954; Cavanagh *et al.*, 1957; Meyer, 1957). The specimens can be arranged into two main groups, both of which can be subdivided. First is a group of 14 cases in which small focal and discrete lesions were found. Prominent among these were a group of tiny tumours consisting of some 9 glial tumours or glial malformations (hamartomas) and 2 capillary angiomas (Group Ia). The remaining cases in this first group consisted of 2 glial infarcts secondary to arterial disease and 1 traumatic cicatrix (Group Ib). The various focal lesions had a predilection to involve the medial and inferior temporal structures such as the amygdala, uncus, hippocampal gyrus, and the temporal pole. In no case was the hippocampus involved.

The second group comprises a series with diffuse and disseminated lesions of a wide range of severity. In the milder ones (Group IIb—15 cases) subpial gliosis and gliosis of the white matter of moderate severity are the only abnormalities found, the cortical layers appearing intact. In the more severe (Group IIa—21 cases), patchy or diffuse nerve-cell loss is seen in the cortex (chiefly layers II and III), in the hippocampus (Ammon's horn), in the uncus, and in the amygdala. The distribution of the neuronal atrophy and the gliosis corresponds well with Penfield's concept of incisural sclerosis (Earle *et al.*, 1953).

*Clinical features correlated with pathological findings.*—We have attempted to correlate with these pathological findings a number of clinical and ætiological factors. There are striking differences in the age of onset of epilepsy in each of our pathological subgroups. Thus in the group of diffuse and disseminated lesions with Ammon's horn sclerosis and cortical atrophy (Group IIa) the average age of onset of epilepsy was 4½ years, in the group of diffuse lesions without Ammon's horn sclerosis (Group IIb) it was 12 years, in the group (Group Ia) with tiny tumours and capillary angiomas it was 23 years, while in the remaining patients (Group Ib) it was 36 years. With one exception, a child of 2½, all our patients were operated on between the ages of 12 and 56, and the mean duration of epilepsy prior to operation ranged from ten years in the case of the tumours (Group Ia) to eighteen and nineteen years respectively in the two subgroups of disseminated lesions.

On further analysis we found that in the group with disseminated lesions there was, besides the younger age of onset, a fairly frequent family history of epilepsy (6 out of 36 cases), a high incidence of difficult birth (11 cases) or of pyrexial convulsive disorders in infancy (14 cases), and a frequent association of slight hemiatrophy of the cranial cavity as seen in skull X-rays. All these points suggest that the lesions arose in early childhood. On the other hand with the focal lesions, which generally do not manifest epilepsy until adult life, there is usually no history forthcoming of difficult birth or of infantile convulsions, while the skull X-rays show no asymmetry.

Some interesting observations were also made with regard to fit patterns, electroencephalographic findings, and the pre-operative personality disorders. Thus *grand mal* occurred in nearly two-thirds of the patients with diffuse lesions, but was rare in the tumour-hamartoma subgroup (Ia). The incidence of the various auras was approximately the same throughout the two groups, an epigastric aura being by far the most common. Dr. Hill has pointed out the EEG significance of diminished barbiturate-fast activity in the inferior temporal regions on one side as indicating pathological changes in that temporal lobe, particularly those associated with Ammon's horn sclerosis (Group IIa). It is also noteworthy that in 4 of the 11 patients with tumour or hamartoma, there was an apparently independent subsidiary focus of spike discharges in the opposite temporal lobe. Such foci disappeared after the lobectomy. This is in keeping with the experimental observations of Gastaut (1953) and of Penfield and Jasper (1954) in that a secondary focus may appear in the opposite temporal lobe after the unilateral injection of alumina cream into the temporal lobe of an animal. It is therefore of interest that independent subsidiary foci were noted in the opposite temporal lobe in a similar proportion of cases with disseminated lesions.

When the varieties of personality disorder were compared with the pathological findings

UNIVERSITY OF MICHIGAN LIBRARIES

certain important points of difference were discerned. Thus, outbursts of aggressive behaviour were noted in more than half the cases with Ammon's horn sclerosis. Again most patients with hysterical personalities were in the subgroup of disseminated lesions without Ammon's horn sclerosis, a subgroup in which the underlying pathological changes could be regarded as minimal. Patients with normal personalities, or with paranoid aggressive or inadequate hysterical personalities occurred in similar proportions in the two main pathological groups. The average I.Q. for all patients was 97, but the range was slightly lower in the Ammon's horn sclerosis subgroup than in the others.

*Therapeutic results of surgery.*—24 of the 50 patients have been completely free of seizures for from two to seven years following operation, while a further 2 patients have had only an occasional seizure, not more than two seizures in any one year. In addition, 12 other patients have been improved by 50%; thus three-quarters of the patients (37 out of 50) can be considered improved. It has been our policy, however, to keep patients on anti-convulsant medication for at least two or three years after operation, although some patients have successfully rebelled against this. We have found that if patients are seizure-free at the end of the first year, they are likely to remain free. However, there have been three exceptions, 1 after head injury, 1 towards the end of a pregnancy, and 1 after some unusual medication. All 3 patients subsequently became seizure-free again.

The most striking degrees of benefit as regards fits were seen in the subgroup of tumours and hamartomas, for all were improved. So far none of these lesions has apparently recurred. Two-thirds of the patients with Ammon's horn sclerosis were improved, but only one-third of those of disseminated lesions without Ammon's horn sclerosis.

All 5 patients with a normal pre-operative personality did well, becoming fit-free and retaining their normal personalities. The improvement of personality in the remaining patients was not so striking as the improvement of the epilepsy. On analysis we noted that patients with aggressive outbursts usually improved both as regards their fits and their personality, and that most of them were in the subgroup with Ammon's horn sclerosis (Group IIa). Patients with inadequate ineffectual personalities or with paranoid disturbances tended to improve as regards their fits but not as regards their personality. Cases with hysterical personality responded poorly on all counts, and were mostly in the subgroup of disseminated lesions without Ammon's horn sclerosis (Group IIb). Whenever there was an improvement in personality, there was also a corresponding improvement in working ability. A more detailed study of the way in which the personality is affected has recently been published (Hill *et al.*, 1957). A long period of rehabilitation is often required in settling a patient who for most of his life has been an epileptic, and is now seizure-free.

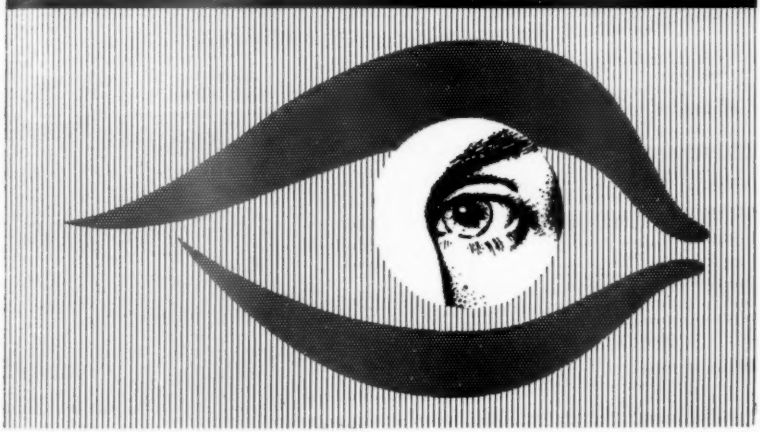
CONCLUSIONS.—From the surgeon's viewpoint the best results are seen in those patients who are disabled by fits, fulfil the necessary electroencephalographic criteria, but have no overt personality disorder. If a personality change is present, those patients who show aggressive outbursts should be operated on. Improvement must not be expected in the mental state of patients who show paranoid aggressive states, hysterical reactions, or inadequate ineffectual personalities. A past history of a psychotic episode, however, does not adversely affect the results. The operation of anterior temporal lobectomy in carefully chosen patients can frequently yield very gratifying results.

*Acknowledgment.*—The author wishes to thank the Medical Research Council for a grant towards the investigation and follow-up of the patients.

## REFERENCES

BALDWIN, M. (1958) Personal communication.
CAVANAGH, J. B., FALCONER, M. A., and MEYER, A. (1957) Proc. 2nd Int. Colloq. on Temporal Lobe Epilepsy, Bethesda, Maryland. Edited by Maitland Baldwin. Springfield, Ill.; in press.
EARLE, K. M., BALDWIN, M., and PENFIELD, W. (1953) *Arch. Neurol. Psychiat., Chicago*, 69, 27.
FALCONER, M. A., HILL, D., MEYER, A., MITCHELL, W., and POND, D. A. (1955) *Lancet*, i, 827.
——, MEYER, A., HILL, D., and WILSON, J. L. (1957) Proc. 2nd Int. Colloq. on Temporal Lobe Epilepsy, Bethesda, Maryland. Edited by Maitland Baldwin. Springfield, Ill.; in press.
——, and WILSON, J. L. (1958) *Brain*, **81**, 1.
GASTAUT, H. (1953) *Epilepsia*, III ser., **2**, 59.
HILL, D., POND, D. A., MITCHELL, W., and FALCONER, M. A. (1957) *J. ment. Sci.*, **103**, 18.
KENNEDY, W. A., and HILL, D. (1958) *J. Neurol. Psychiat.*, **21**, 24.
MEYER, A. (1957) In: Modern Trends in Neurology. Edited by D. J. Williams. London; p. 301.
——, FALCONER, M. A., and BECK, E. (1954) *J. Neurol. Psychiat.*, **17**, 276.
MEYER, V., and JONES, H. G. (1957) *J. ment. Sci.*, **103**, 758.
——, and YATES, A. J. (1955) *J. Neurol. Psychiat.*, **18**, 44.
PAMPLIGLIONE, G., and KERRIDGE, J. (1956) *J. Neurol. Psychiat.*, **19**, 17.
PENFIELD, W., and JASPER, H. (1954) Epilepsy and the Functional Anatomy of the Human Brain. London.
PICAZA, J. A., and GUMA, J. (1956) *Arch. Neurol. Psychiat., Chicago*, **75**, 57.

**the antibiotic of choice**
**in a NEW presentation**



## ACHROMYCIN OPHTHALMIC OIL SUSPENSION 1%

has been specially developed to make the topical use of ACHROMYCIN tetracycline in eye infections even simpler and more effective. The Oil Suspension offers optimal dispersion of the antibiotic; it diffuses rapidly into the conjunctival sac, has less effect on visual acuity and provides longer-lasting antibiotic effectiveness.

This new form of ACHROMYCIN is acceptable in every sense—to patient and physician alike. The new plastic dropper-type bottle makes accurate dosage easy, and the preparation is virtually free from side-effects. Because the product is so effective and simple to use, the patient can co-operate fully in following the treatment prescribed. That is why ACHROMYCIN Ophthalmic Oil Suspension 1% is now the treatment of choice in many forms of eye infection.

# ACHROMYCIN*

TETRACYCLINE *REGD. TRADEMARK

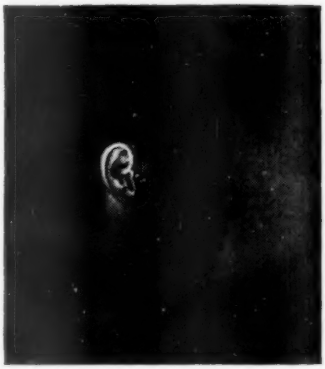
## OPHTHALMIC OIL SUSPENSION

Each cc. of ACHROMYCIN Ophthalmic Oil Suspension contains Tetracycline HCl 10 mg.; Ethyl Cellulose 20 mg.; Tocopherol in Oil 34%, 0·0015 cc.; Sesame Oil to 1 cc. In plastic dropper-type bottles of 6 cc.

Lederle LEDERLE LABORATORIES DIVISION
*Cyanamid* OF GREAT BRITAIN LTD., London, W.C.2

# EAR WAX

## *Removed this easy way*



The removal of wax from the external auditory meatus has, in the past, normally entailed attendance by the patient for diagnosis and for the prescription of a suitable loosening agent, and a second attendance a few days later for syringing.

Now, by the use of Cerumol Ear Drops, wax can be removed in most cases at one visit. A few drops of Cerumol can be instilled into the ear and, while another patient is being attended to, the soft cerumen dissolves and the harder wax disimpacts. The wax can then be removed by gentle syringing or with cotton wool. The wax may even be found to run out of the ear on its own accord, in which case patients themselves may instil Cerumol at home, obviating further attendances.

Cerumol is anti-bacterial, non-irritating and harmless to the lining of the external auditory meatus or the tympanic membrane.

Cerumol is included in Category No. 4 of the M.O.H. classified list and may be prescribed on N.H.S. Form E.C.10.

**CERUMOL**
Regd TRADE MARK

***EAR DROPS***

*for the easier removal of wax*

*PACKS For Surgery Use: 10 c.c. vial — separate dropper included (Basic N.H.S. price 2/8) for Hospital Use: 2 oz. and 10 oz. bottles.*

*If you wish to test for yourself and have not received recently a 10. c.c. vial please write or telephone direct to:*
**LABORATORIES FOR APPLIED BIOLOGY LTD.,**
**91, AMHURST PARK, LONDON, N.16 Tel.: STA 2252**

# Section of Otology

President—I. SIMSON HALL, F.R.C.P.Ed., F.R.C.S.Ed.

[*February* 7, 1958]

A DISCUSSION on **Cholesteatosis of the Attic** was opened by Professor L. RÜEDI (Zurich), Mr. I. A. TUMARKIN and Dr. J. F. BIRRELL.

Dr. I. FRIEDMANN, Mr. T. E. CAWTHORNE, Mr. I. B. THORBURN, Mr. F. MCGUCKIN, Mr. R. SIMPSON and Mr. P. H. BEALES also took part in the discussion.

The meeting will be reported in the *Journal of Laryngology*.

[*March* 7, 1958]

THE following short papers were read:

**Congenital Atresia of External Auditory Meatus.**—Mr. GAVIN LIVINGSTONE.
**Surgery of Congenital Atresia of External Auditory Meatus.**—Mr. H. S. SHARP.
**Endaural Surgery of the Jaw-joint.**—Mr. A. S. DAVIDSON.
**Hearing Problems in a Baby.**—Mr. N. L. CRABTREE.
**Tetanus from Marine Sponge.**—Mr. LIONEL TAYLOR.

The papers were discussed by Mr. DAVID BAWTREE, Mr. F. MCGUCKIN, Mr. H. V. FORSTER, Mr. I. A. TUMARKIN, Mr. E. D. D. DAVIS, Mr. R. G. HUGHES, Mr. I. SIMSON HALL, Mr. R. G. MACBETH, Mr. S. W. ALLINSON, Mr. T. B. LAYTON, Mrs. F. CAVANAGH, Mr. H. S. SHARP, Mr. L. FISCH and Mr. R. L. FLETT.

The meeting will be reported in the *Journal of Laryngology*.

[*May* 2, 1958]

## DISCUSSION ON THE CONSERVATIVE MANAGEMENT OF MÉNIÈRE'S DISEASE

**Dr. R. B. Lumsden** (Edinburgh): *Treatment of Ménière's Disease with Ultrasound*

The practical application of ultrasound was initiated in France in a wartime academic atmosphere when Langevin, in 1916, began the study of underwater echo (Wakim, 1953) and first conceived the ultrasonic quartz/steel transducer as it is known to-day. Further explorations were carried out, both in Britain and the U.S.A., at that time (Klein, 1948). Between 1928 and 1932 attempts to treat deafness with ultrasound afforded no convincing results (Mülwert and Voss, 1928; Voss, 1933). In 1949 Wiethe and his co-workers in Vienna reported encouraging results by improved methods of application. Further reports, however, continued to be contradictory. Naumann (1955), for example, has found no benefit from this method and draws attention to the potential dangers of ultrasonic therapy. On the other hand, experimental studies of the action of ultrasound on the inner ear in guinea-pigs demonstrated the possibility of applying it to a restricted part of the inner ear (Krejci and Bornshein, 1951); and Krejci in 1952, after surgical exposure through the mastoid cavity in Ménière's disease, subjected the lateral semicircular canal to direct application of ultrasound with resulting suppression of vestibular function and slight improvement in hearing.

My interest in ultrasound was first aroused by the Presidential Address which Air Vice-Marshal Dickson gave to this Section in November 1952 (Dickson, 1953). That interest became focused on its use in the treatment of Ménière's disease as a result of observation of the work of Professor Arslan in Padua (Arslan, 1953*a*, *b*); and a small series of 22 cases, which I have treated by his method, forms the basis of this communication.

Before proceeding to a description of the technique of this treatment it is important to define briefly its status in relation to other methods of applying ultrasonic therapy in aural disease. Professor Portmann and his co-workers in Bordeaux (1954) have published a comprehensive and critical account of ultrasonic therapy as applied in otolaryngology.

*Three routes of access of ultrasound to the ear are described*:

(1) *External, transmastoid.*—This is a bad technique for several reasons, the chief one being based on the fact that *ultrasonic waves do not pass from a solid or liquid medium to air or vice versa*, since reflection occurs at the interfaces. Therefore, by the transmastoid route, since the axis of the beam passes across the air-containing mastoid cavity, the waves are scattered before reaching their objective.



UNIVERSITY OF MICHIGAN LIBRARIES

(2) *Surgical*, in which direct access is afforded through a modified cortical mastoid operation cavity—Arslan's method. This is ideal for a single, destructive application to the posterior labyrinth.

(3) *Transmeatal* (Portmann *et al.*, 1954), in which a watertight system in the external auditory meatus provides the medium for transmission. It is claimed that this method combines the ease of the external method and the precision of direct surgical access, without their disadvantages. It entails repeated applications of relatively low intensity; its basic conception is somewhat different and so far we have no experience of it.

*The Arslan technique*, then, may be defined as the direct application to the posterior labyrinth of ultrasonic waves by which means vestibular function can be attenuated or completely eliminated *without impairing cochlear function.*

It might be said that a procedure involving a mastoid operation of access cannot be regarded as conservative, but surely the preservation of hearing which it affords is sufficient justification for classifying it thus.

*The apparatus* employed is of Italian origin and, while I shall not attempt to describe its components, a few features require to be mentioned:

The *frequency* is approximately 800,000 cycles per second. *Intensity* is measured in watts per square centimetre and a dosimeter indicates the effective power emitted by the applicator (erogator, transducer). A centrifugal pump circulates fluid in order to cool the piezo-electric element which generates the high frequency sound waves.

The *special applicator* has an active surface of 0·2 sq. cm. and can deliver up to 12·5 w./cm². A vital feature of its design is the elimination of any lateral transmission of energy.

### *Description of Arslan's Procedure*

As we shall see, it is essential that the procedure is carried out under local anæsthesia. For this purpose we infiltrate with lignocaine hydrochloride (2% with adrenaline 1:80,000).

Concerning sedation, Arslan employs premedication with morphine. In our experience the co-operation and presence of an anæsthetist has proved invaluable and our preference is for pethidine in an initial dose of 100 mg. I.V. given slowly in dilute solution (5 c.c.) and repeated as required in doses of 20 mg. In this manner a total dosage of up to 350 mg. has been given during the operation. An hour or so before operation a test dose of 50 mg. is given I.M. An important advantage of pethidine is that in Lethidrone (in doses up to 4 mg.) we have a specific antidote with which the patient can be roused as required during the operation. We have failed to get sufficient co-operation when giving pentobarbitone or chlorpromazine (for which there are no adequate antidotes).

Through a post-auricular incision a limited cortical mastoid exposure is made, of such extent as to afford free direct access to the lateral semicircular canal. If necessary, the immediate surrounding bone is reduced slightly so as to bring the canal into relief, but care is taken to avoid any contact with the incus.

Thorough hæmostasis is now demanded and a small aspirating tube within the mastoid cavity is a valuable precaution, since it is essential that the area of contact between the lateral canal and the ultrasonic applicator should be completely dry.

We are now ready to proceed with the ultrasonic application and it is necessary to rouse the patient in order to enlist his co-operation. From now on two additional assistants are essential—one to observe constantly the patient's reactions and the other to control the apparatus.

The flat tip of the ultrasound applicator is firmly applied to the convexity of the lateral canal. Its line of axis must be studied so that irradiation of the cochlea or facial nerve is avoided and it must be strictly co-axial with the canal. (Discussion of further refinements of axial control are fully discussed in Arslan's descriptions (Arslan, 1953*a*, *b*; 1957*b*).)

Throughout this period the assistant whose duty it is to observe the occurrence and nature of nystagmus should also observe facial nerve function. Any isolated contractions or weakness would, of course, warrant immediate suspension of irradiation.

*Nystagmus.*—This usually appears two or three minutes after irradiation commences. Initially it is towards the side being treated, i.e. "irritative" in type. This lasts for a few minutes, after which there follows a period during which nystagmus is entirely absent. In due course nystagmus to the opposite side appears, i.e. "paralytic" type. This is regarded as an indication that an irreversible effect has been attained.

*Dosage.*—This cannot be rigidly pre-determined, but varies somewhat with the course of the nystagmus. In the early period the average duration was fifteen minutes; intensity commenced at 3–5 w./cm² and increased to 7–8 w./cm². Later (Arslan, 1957*a*), both intensity and duration have been increased considerably and at present our average dosage consists of a gradual rise up to 8 w./cm² at ten minutes, increasing up to 10 w./cm² at fifteen minutes and maintained for a total duration of thirty minutes.

In a few cases, notably when vestibular excitability is already markedly reduced, the usual

features of nystagmus may not appear, in which case dosage must be controlled on a basis of intensity/time average.

At the termination of irradiation the mastoid wound is completely sutured.

The one complication which requires comment is facial paresis: Arslan (1953*b*) reported two such occurrences in his early series, and subsequently reports complete recovery in all his cases (1957*a*). It occurred in three of my series, all of whom recovered and to whom I shall refer later.

*The post-operative course.*—When compared with the condition of cases after surgical elimination of labyrinth function, this is quite remarkable. It is usual for the patient to be comfortably sitting up in bed on the day after operation. Sickness is practically unknown and nystagmus disappears within twenty-four to forty-eight hours after operation. The occasional occurrence of modified attacks of vertigo during the first few weeks is not an indication of failure, but suggests a progressive degenerative process rather than an immediate totally destructive one. Head exercises are, of course, beneficial at this stage, especially in older people.

### *Biological Effects of Ultrasound*

The biological effects of ultrasound may be classified under three broad headings, namely —mechanical, thermal and chemical; the relative importance of these three is still not clearly defined. Indeed it seems possible that this may vary in different circumstances. Moreover, it is not yet clear to which of these effects some of the recognized phenomena are due, e.g. the formation of gas bubbles resulting in the condition known as "cavitation" (*see* Wakim, 1953; Portmann *et al.*, 1954).

While accepting that the biological and therapeutic effects are still far from being clearly understood we do know that the effect on living tissue may be temporary and reversible with weak or so-called "therapeutic" doses; or progressive and destructive with stronger doses. It is also known that the margin between these doses is small and that tissues vary in their degree of sensitivity to ultrasound, nervous tissue being particularly sensitive (Fry, 1954).

In the treatment of Ménière's disease the object of Arslan's method is essentially selective destruction, while the Portmann technique is described, in contrast, as "therapeutic".

If an area made up of tissues of varying densities is irradiated, the effects are greatest at the interfaces, i.e. at the level of changes in tissue density. In this connexion it is instructive to contrast the distribution of heat in bone, for example, when produced by short-wave diathermy and ultrasound: with s-w diathermy heat is distributed uniformly throughout the exposed tissue, while the thermal energy of ultrasound is mainly concentrated at the periphery. Consequently periosteum and endosteum show the initial and more intense reaction. Several studies have shown appreciable local rise of temperature in bone (Bender *et al.*, 1953; and *see* Wakim, 1953).

*The histological effects of ultrasound on the labyrinth.*—These have been described by a number of workers employing different methods of application and dosage (Krejci and Bornshein, 1951; Portmann *et al.*, 1954; Naumann, 1955). They vary from hyperæmia to tissue destruction. Of special interest are the reports of de Stefani (1956) and Arslan (1955), who have shown that irradiation of the labyrinths of dogs resulted in destruction of the cells of the neuroreceptive epithelium of the ampullary crista. No changes were found in the cupola and slight hyperæmia was the only finding in the canal perilymphatic space, suggesting that the nervous portion of the vestibular organ is most sensitive to ultrasound. They also suggest that the lesions are probably due to thermal rather than to mechanical effect.

In Edinburgh, at the present time, we are engaged in a small experimental programme in which application of ultrasound (u-s) by Arslan's method has been made to the labyrinths of cats. The resulting histological material has not yet been investigated, but a preliminary report on certain observations can now be made:

Relatively high dosage was employed (up to 10 w./cm² for fifteen minutes), yet no macroscopic intracranial lesions have been noted, such as those reported by some observers using different techniques and intensities (Portmann *et al.*, 1954; Naumann, 1955).

Of the temperature investigations carried out, two might be mentioned:

(i) A thermocouple was placed in the vestibule of a fresh human temporal bone partly immersed in a water bath at 38° C. Ultrasound was applied in the usual manner and a rise of 9 C. was recorded.

(ii) In a somewhat similar experiment on the live cat, the application of a relatively high intensity of u-s resulted in a rise of 25° C.

*The post-operative clinical features.*—These have been more marked and prolonged in cats than in human beings. Well-marked nystagmus to the opposite side persists for four to five days. They are able to stand within thirty-six hours, but there is a marked tendency

to fall towards the treated side when walking. This tendency was still present, though much less marked, at the end of three weeks—the longest period of observation. Facial weakness was observed on several occasions, which anatomically is not unexpected.

I am indebted to our President for a brief ciné film illustrating the behaviour of the cat after ultrasonic therapy.

*Clinical Results*

Before discussing results, it is important to remember: (1) that exhaustive medical treatment has invariably been employed before ultrasonic therapy is resorted to; and (2) that its fundamental object is the cure of paroxysmal vertigo with preservation of hearing.

In his first series of 195 cases, Arslan (1957*b*) reports success at the end of one year in 184 (94%). He draws attention, however, to the presence, in a proportion of essentially successful cases, of those transient and somewhat vague subjective disturbances encountered in otherwise controlled cases.

In my small series, such symptoms have been observed mainly in older patients. Undoubtedly much depends on trying to assist these people to regain their shaken confidence during the establishment of compensation.

A preliminary report from Zürich (Dubs, 1957) concludes that Arslan's method of ultrasonic therapy is probably superior to all other forms of treatment of Ménière's disease.

Between August 1956 and August 1957 I have treated 22 cases by this method. Table I presents a pre-operative analysis of these cases:

TABLE I

*Sex:* Male 16, Female 6

*Affected ear:* Right 10, Left 12

*Age:* Youngest 21, Oldest 79, Average 47 years

*Duration of symptoms:* Shortest 6 months, Longest 22 years, Average 5 years

*Pre-operative audiogram* (average for 500, 1,000 and 2,000 c/s)
Smallest loss 10 db., Greatest loss 75 db., Average loss 45 db.
(average post-operative loss was also 45 db.)

*Recruitment:* Recorded in 16 cases—Present in 15
Absent in 1 (successful)

*Pre-operative caloric vestibular tests:*

| | |
|---|---|
| Canal paresis | 13 |
| Preponderance to opposite side | 2 |
| Normal | 6 |
| Pre-existing modified radical mastoid: marked response to cold air | 1 |

In assessing results to date, I have classed as "successful" those cases which are free from paroxysmal vertigo and have been able to resume their normal employment without subsequent interruption or, in the case of older patients, to indulge freely in activities appropriate to their age.

In Table II cases have been placed in two groups: (i) those followed up for twelve to eighteen months, and (ii) those treated less than twelve, but more than six months ago.

TABLE II

| Result | 12–18 months | 6–11 months | Total |
|---|---|---|---|
| No paroxysmal vertigo | 5 | 10 | 15 |
| Improved—modified attacks | 2 | 2 | 4 |
| Unchanged | 1 | 2 | 3 |
| | 8 | 14 | 22 |

Of the 4 cases which continue to have modified attacks, 2 were almost certainly undertreated and one has subsequently shown signs of the other side being affected. I have not yet applied treatment bilaterally, but Arslan (1957*b*) reports having successfully treated the second side after an interval of six months, in 3 cases. One of my 3 cases in which no improvement was obtained had, years previously, undergone a successful modified radical mastoid operation and ultrasonic treatment was applied through an endaural exposure. I now believe that this resulted in faulty application, due to restricted access and it has not yet been possible to repeat the application by a posterior approach. Another apparent failure has subsequently shown signs of the other side being affected.

I have already referred to the possible recurrence of modified attacks during the early post-operative period. One so-far successful case experienced quite a severe attack at the end of three weeks and continued to have slight positional vertigo for three months, but

has subsequently resumed work as a bus driver. He exhibited a minimal caloric response ten months after treatment. Arslan (1957*b*) also finds that some successful cases retain a minimal response to caloric stimulation.

Table III records my findings in this respect:

TABLE III

| Symptomatic result | | Cold caloric reaction | |
|---|---|---|---|
| Successful (to date) | 15 | Absent .. .. .. .. | 11 |
| | | Minimal .. .. .. | 4 |
| Improved .. .. | 4 | Absent .. .. .. .. | 1 (bilateral) |
| | | Minimal .. .. .. | 2 (? under-dosage) |
| | | Preponderance to affected side | 1 |
| Unchanged .. | 3 | Absent .. .. .. .. | 1 (bilateral) |
| | | Marked .. .. .. | 1 (? faulty technique) |
| | | (Not known .. .. .. | 1) |
| | 22 | | 22 |

The one "improved" case with directional preponderance is of special interest: immediately prior to u-s therapy she had normal differential caloric reactions, though two years previously she had shown directional preponderance towards the affected side. Recruitment was present. For six months after treatment the caloric reaction was absent on that side, but at eight months she shows a preponderance towards the affected/treated side. Meanwhile hearing has fluctuated from 35 to 55 db. and at eight months is 35 db., 10 db. worse than before treatment. The duration of therapy was five minutes below the present average.

Of the first 4 cases treated, 3 showed little or no improvement and it was obvious that they had received inadequate dosage. Treatment was repeated in these 3 cases (after intervals of four, eight and five months). The second application so far has been successful in 1 (ten months) and attacks have been appreciably modified in another (fourteen months) in which dosage is again thought to be inadequate. One remains unchanged.

TABLE IV.—EFFECT OF U-S ON TINNITUS

| | | |
|---|---|---|
| Persistent tinnitus present before treatment in 18 cases. | | |
| Following u-s treatment: | No tinnitus | 0 |
| | Tinnitus improved | 7 (6 free of vertigo) |
| | Tinnitus unchanged | 11 |
| No complaint of tinnitus before treatment in 4 cases. | | |
| Following u-s treatment: | Free of vertigo | 3 |
| | Improved | 1 |

TABLE V.—EFFECT OF U-S ON HEARING

| Hearing (Average for 500, 1,000 and 2,000 c/s) | | Vertigo: Nil | Improved | Unchanged |
|---|---|---|---|---|
| Improved | 1 (10 db.) | — | 1 | — |
| Unchanged (+ or −5 db.) | 15 | 11 | 2 | 2 |
| Worse | 5 | 4 | 1 | — |
| (Not known | 1 | — | — | 1) |

Of the 5 cases in which hearing is worse, the reduction has been 10 db. in 3, 15 db. in 1 and 20 db. in 1. Neither the pre-operative hearing level nor the ultrasonic dosage would appear to offer any explanation for the deterioration in these five particular cases, when compared with others in the series.

Arslan reports more favourably concerning both post-operative hearing and tinnitus. Undoubtedly some of my cases were very advanced, but it is worth noting that in 7, repeated audiograms have shown fluctuations in hearing (and associated tinnitus) in the region of 15 to 20 db. 5 of these are free from paroxysmal vertigo, while 2 have modified attacks; and though they have had periods of improved hearing, such fluctuations certainly do not justify their classification as consistently "improved". Indeed, one wonders whether their ultimate fate may not be that of overall progressive deterioration of hearing.

Figs. 1 and 2 illustrate such fluctuations.

*Facial paresis.*—This is shown to be a hazard, but with experience and the observation of precautions already mentioned, it should be an infrequent occurrence, followed by complete recovery (Arslan, 1953*b*, 1957*a*). Its occurrence three times in my small series may appear to suggest an excessive risk, but it is to be noted that of Arslan's few cases, the majority occurred during his earlier experience.

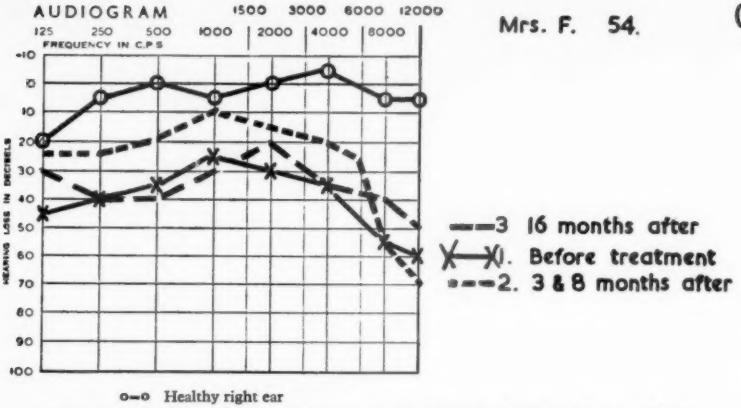



FIG. 1.—Ménière's disease, left ear. Fluctuations in hearing after u-s therapy.

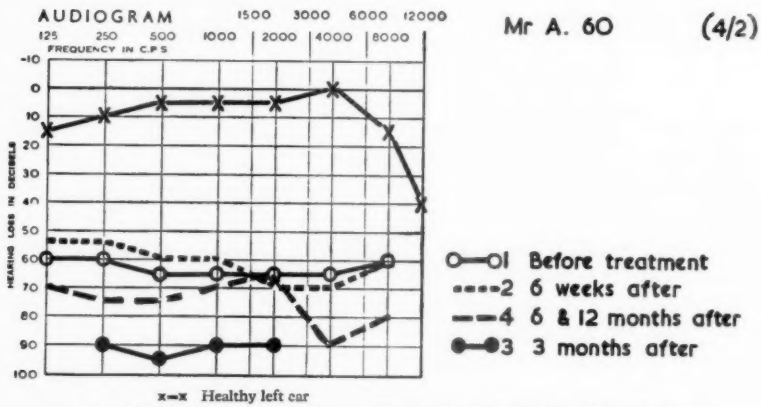



FIG. 2.—Ménière's disease, right ear. Fluctuations in hearing after u-s therapy.

TABLE VI

| Time of onset | Degree | Recovery | Post-operative: Vertigo | Post-operative: Caloric reaction | Post-operative: Hearing |
|---|---|---|---|---|---|
| 1. Two days after *repeat* application | Slight | 2–3 weeks | Unchanged | ? | ? |
| 2. Near end of application (12 w./cm²) | Severe | Commencing at 3/12. Complete at 6/12 | Nil | Nil | Worse, variable |
| 3. Temporary at 5 min. (8 w./cm²) Reappeared during next 24 hours | Severe | Commencing at 3/12. Complete at 6/12 | Nil | Nil | Unchanged |

The three cases of facial paresis encountered merit further consideration (Table VI).

The course of events in the third case require particular mention: at the end of five minutes both irritative and paralytic nystagmus had appeared in turn—an unusually early occurrence, with a subsequent successful result, showing that dosage had been adequate in spite of its very short duration. Attention was drawn to the initial onset of facial weakness by the

patient and by the two observers at the same instant and u-s application ceased immediately. By the time the wound was closed facial weakness had completely passed off, but recurred progressively during the succeeding twenty-four hours.

The findings which have been presented are essentially in the nature of an interim report and require a close follow-up over several years. In the meantime, the following general commentary is submitted:

It will be appreciated that in a fairly high proportion of our cases, particularly those treated at the commencement of the series, symptoms were of such duration and severity and the hearing loss so great that some completely destructive procedure could very justifiably have been employed. At that stage of one's experience it was reassuring to find that cases with a loss of 60 or 70 db. could, in fact, retain even that amount of hearing after u-s therapy.

We can next consider a group of 7 cases with a loss no greater than 30 db., all of which are, so far, free of vertigo; hearing results are shown in Table VII.

TABLE VII.—HEARING IN 7 CASES, ALL FREE OF VERTIGO
(Average for 3 speech frequencies)

| Before treatment | 6–16 months after treatment |
|---|---|
| 30 db. | 30 db. (variable) |
| 20 | 15 |
| 25 | 35 |
| 25 | 35 (variable. Facial paresis) |
| 10 | 10 (facial paresis) |
| 20 | 35 (variable) |
| 30 | 25 |
| Average 23 db. | 26 db. |

Despite the slight overall loss, it would appear that these cases have so far derived comparative benefit from this method of treatment. Furthermore, as far as the evidence goes, there would seem to be justification for intervention with u-s therapy at an earlier stage than that at which the recognized destructive procedures are commonly resorted to.

As to whether u-s therapy is a procedure of choice when a severe degree of deafness already exists, only further experience will tell. On the other hand, it would appear to offer a possible useful alternative in certain bilateral cases. Lastly, I believe that with increasing experience, better results will be achieved.

I wish to acknowledge my indebtedness to a large number of people from whom I have received much help and advice. I would offer special thanks to Professor Arslan for according to me, in such full measure, the fruits of his experience; to the President and other otological colleagues and Dr. M. C. MacQueen, anæsthetist, for their co-operation, encouragement and forbearance; to our assistants, for their help with so many routine investigations; and to Dr. J. M. Johnston of the Department of Health for Scotland, for his informed advice and for guiding me through the perils of acquiring an ultrasonic apparatus.

I am also grateful for the facilities afforded in the Wilkie Surgical Research Laboratory and by the Ferens Institute.

## REFERENCES

ARSLAN, M. (1953*a*) V *Congr. int. Oto-rhino-laryng.*, 429.
—— (1953*b*) *Minerva otorinolaring.*, **3**, 141.
—— (1955) *Z. Hals- Nas.- u. Ohrenheilk.*, **167**, 559.
—— (1957*a*) Personal communication.
—— (1957*b*) *J. franç. Oto-rhino-laryng.*, **6**, 833.
BENDER, L. F., JANES, J. M., and HERRICK, J. F. (1953) Proc. 38th Clin. Congress, Amer. Coll. Surg. Philadelphia.
DICKSON, E. D. D. (1953) *Proc. R. Soc. Med.*, **46**, 139.
DUBS, R. (1957) *Pract. oto-rhino-laryng.*, **19**, 401.
FRY, W. J. (1954) *J. ment. Sci.*, **100**, 85.
KLEIN, E. (1948) *J. acoust. Soc. Amer.*, **20**, 601.
KREJCI, F. (1952) *Pract. oto-rhino-laryng.*, **14**, 18.
——, and BORNSHEIN, H. (1951) *Arch. ital. Otol.*, **62**, 1.
MÜLWERT, H., and VOSS, O. (1928) *Arch. Ohr.-, Nas.-, u. KehlkHeilk.*, **119**, 81.
NAUMANN, H. H. (1955) *Eye, Ear, Nose Thr. Mon.*, **34**, 184.
PORTMANN, G., PORTMANN, M., and BARBE, L. (1954) Soc. franç. d'oto-rhino-laryng. Congrès de 1954. Rapports: 61, 5. Paris.
STEFANI, G. B. DE (1956) *Arch. ital. Otol.*, **67**, Suppl. 27.
VOSS, O. (1933) *Arch. Ohr.-, Nas.-, u. KehlkHeilk.*, **135**, 258.
WAKIM, K. G. (1953) *Amer. J. Phys. Med.*, **32**, 32.
WIETHE, C., WYT, L., and VYSLONZIL, E. (1949) *Acta otolaryng., Stockh.*, Suppl. 78.

**Mr. M. Spencer Harrison** (Lincoln) and **Dr. L. Naftalin** (Lincoln): *Dietary Electrolytes in Ménière's Disease*

A little over two years ago Roland Lewis and one of us (M. S. H.) gave the Section details of 43 patients with Ménière's disease who had been treated by cervico-dorsal sympathectomy during the previous five or more years (Lewis, 1956; Harrison, 1956). We have again reviewed these patients (Tables I, II and III).

TABLE I.—TIME SINCE OPERATION IN YEARS

| King's to | 1, | 2, | 3, | 4, | 5, | 6, | 7 years | > 7 years |
|---|---|---|---|---|---|---|---|---|
| | | | 2 | 8 | 1 | 4 | 6 | 8 |

M.S.H. All 6–7 years except 2 bilateral cases, one of which is still improved $3\frac{1}{2}$ years after operation.

TABLE II.—VERTIGO

| | | King's | King's Total cases | M.S.H. | M.S.H. Total cases |
|---|---|---|---|---|---|
| Bilateral cases | Vertigo ceased or much improved | | | 1 | |
| | Vertigo improved .. .. .. | 4 | 10 | 3 | 5 |
| Unilateral cases | Vertigo ceased or much improved | 9 | | 8 | |
| | Vertigo improved .. .. | 4 | 18 | 1 | 9 |
| | | 17 | 28 | 13 | 14 |

TABLE III.—OVERALL ASSESSMENT

| | | King's | | M.S.H. |
|---|---|---|---|---|
| Much improved | worth-while | 8 | 18 | 10 |
| Improved | benefit | 10 | | 1 |
| Worse or *in statu quo* | | 11 | | 3 |
| | | 29 | | 14 |

The hearing has fallen off in 2 of the Lincoln cases, is unchanged in 8 and better in 4 cases. In 2 bilateral cases the hearing, whilst being maintained on the operated side, has fallen off markedly on the opposite side. Tinnitus is little changed in 9 cases, has improved in 4 and is worse in 1. From these results it does appear that there is a place for sympathectomy in the treatment of Ménière's disease, particularly in bilateral disease in which the hearing is falling off on both sides.

We have recently suggested that circulation of the labyrinthine fluids may occur from the perilymph spaces to the stria vascularis by way of the cochlear duct. If this is true, distension of the scala media would result from a reduced secretion of perilymph and not an over-secretion of endolymph and it might follow that reduction in the intake of fluid would still further reduce the available perilymph.

The publications of Dederding (1929), Mygind and Dederding (1938), and Mygind (1943) constituted the first approach to the biochemistry of the labyrinthine fluids. They started with the premise that Ménière's disease resembles glaucoma and is a hydrops of the labyrinth, originating, they postulated, in a nutritional disturbance produced by capillary dysfunction with a resultant defective oxidation and increase in water-binding efficiency in the cells with subsequent intracellular œdema. They succeeded in relieving many cases, but the treatment did not strike at the origin of the trouble, namely, the cause of the localized accumulation of fluid in the labyrinths of patients with an otherwise normal metabolism.

Furstenberg (1936) and his colleagues (1934) reinvestigated the problem and produced evidence which indicated that a retention of sodium salts was of greater pathological significance than a retention of water in the production of symptoms. The concentration of electrolytes and the degree of hydration of the blood was not reported in any of these communications, and it was left to Talbott and Brown (1940) to show that in 4 patients during an attack the serum potassium was raised and the sodium was lowered, whereas in 44 patients between attacks the concentrations of sodium, potassium, calcium, chlorides, carbon dioxide, phosphate, protein and non-protein nitrogen were normal, and there was no change in the acid-base equilibrium of the blood in Ménière's disease. They administered sodium salts, including the bicarbonate, orally and parenterally without precipitating an attack, and thus concluded that the idea that the symptoms were due to gross retention in the body of water or of sodium chloride must be abandoned, because if such were so, changes—not in practice found—would be present in the relative concentrations of sodium, protein and water in the plasma. This conclusion, however, makes no allowance for the equilibrating changes which may take place between these plasma constituents and the total body pools. Talbott and Brown (1940) explained the clinical

benefits of their diet by stressing the importance of the potassium content of the blood, since it has been observed to vary in certain diseases in which the conduction of nerve impulses is disturbed. Normally the proportions of sodium and potassium in the diet are equal, but a relative increase in the potassium is inevitable in Furstenberg's regime. Since this diet is effective they investigated the combination of a normal diet supplemented with extra potassium 6–10 grams (equal, approximately, to 80–134 mEq.) potassium chloride daily, and found this an apparently successful method of therapy. Other authors, e.g. Walsh and Adson (1940), have recorded similar results.

More recently Perlman *et al.* (1953) found, in their series of cases with Ménière's symptomatology, that low serum sodium increased the intensity of the symptoms, and that raising the serum sodium concentration to normal relieved the condition. Unfortunately, insufficient details of the clinical findings in the patients treated by Perlman are available.

The variability of the results with different dietary regimes seems to warrant a re-examination of the pathological and biochemical data on which the regimes have been based.

Crowe's (1938) explanation of the dilatation of the endolymph system was that a continued secretion of endolymph of raised ionic concentration was possibly responsible for the increased fluid volume by water transfer from perilymph. This can hardly be so in that the production of a fluid of high osmotic tension requires more metabolic work to be done and this continuous increase of work is unlikely by damaged cells. The stria vascularis, considered to be the most probable side of formation of the endolymph, is least damaged in Ménière's disease and may therefore continue to secrete. However, the theory of increased osmotic tension demands increased secretory activity (of a fluid of high potassium content) and histologically no confirmation—such as hypertrophy of the cells of the stria vascularis or of increase in its blood supply—has been noted. A further objection to the idea of the secretion of a fluid of high ionic concentration is that across a cell membrane of this nature transfer of water and ions is two-way, to attain the "steady state", and if extracellular pressure (hydrostatic and osmotic) increased on the cells of the stria vascularis, reabsorption of fluid cannot be considered improbable, providing the increased osmotic tension is due to small particles of the size of sodium and potassium ions. If a high osmotic tension is to be found in the endolymph in Ménière's disease, it is more likely to be associated with the breakdown of high molecular weight compounds to multiple particles of lower molecular weight, than with inorganic ions; these substances would come from the obviously degenerating cells which are unable to perform the metabolic work necessary to maintain normal structure.

The part electrolytes might play in the causation or suppression of symptoms in Ménière's disease may still be of considerable importance even if the osmotic changes and dilatation of the endolymphatic system are not primarily a matter of electrolyte secretion. Other workers have thus considered that patients with Ménière's disease were improved by loading the organism either orally or intravenously with sodium, or orally with potassium. The assumptions made were that body content of sodium and potassium could be significantly altered; that, with the dosages employed, the alteration could be maintained for long periods of time; and that changes, comparable to those produced in the body content of electrolytes, took place also in the endolymph.

More has recently been learned regarding the homeostasis of body electrolytes, particularly in relation to renal mechanisms and the influence of steroid hormones. Further, it is now known from the work of Mr. C. S. Hallpike and his colleagues that the endolymph is an actively secreted fluid of a so-called "intracellular" character, i.e. having a high potassium concentration (Citron *et al.*, 1956) and cannot be a plasma transudate influenced simply and directly by changes in plasma concentrations. Other points which should be borne in mind when considering the relation of electrolyte metabolism to Ménière's disease are the difficulty of describing how a general body change, such as a change in plasma or body concentration of electrolytes, can produce an asymmetrical lesion unless there is also a local pathology; and, as a corollary, if indeed there be a "primary" pathology to be influenced by electrolyte changes, this influence will be at a maximum during acute episodes of the primary lesion and will be of less importance during quiescent periods, and possibly, of little importance when the degenerative process has become more advanced and "stabilized".

It is possible that the clinical improvement recorded in patients with Ménière's disease after treatment with, e.g., low dietary sodium, was dependent only on the fact that the patients concerned felt reassured that some real interest was being taken in their complaint, and their confidence was restored. This restoration of confidence may be an important factor to be considered in assessing the onset of a remission. On the other hand, since it can be demonstrated in short-term experiments that there is to some degree a reciprocal sodium-potassium relationship in the body, in that a loading with one ion leads to the excretion of the other—termed the "Bunge phenomenon" by Gamble (1951)—the improved clinical condition resulting from a low sodium diet, i.e. a relative potassium loading, could possibly be equally achieved by a high potassium loading and a normal sodium intake.

It is not unlikely that repeated acute episodes, involving vomiting attacks with concomitant urinary loss of potassium, may result in a state of chronic potassium deficiency. Even without actual vomiting the anxiety state with attacks of vertigo may cause increased adrenal activity and potassium excretion. The correction of potassium depletion could, by itself, account for some of the increased feeling of well-being experienced by patients to whom this treatment has been given.

Low sodium intake and high potassium supplement have been the most widely practised forms of dietary treatment and, as a first step in assessing their value, we undertook treatments involving ion loading and depletion, observations being made clinically to determine either improvement or increase in intensity of the symptoms. First of all preliminary results are presented of the treatment of 2 patients in whom the diagnosis of Ménière's disease had been established and who were experiencing very frequent vertiginous attacks. Though Ménière's disease is a relatively common condition it is seldom one can find a patient having very frequent attacks as was necessary at the commencement of this investigation. It was decided, therefore, to undertake a particularly detailed investigation of the following 2 patients only, in the first stage of this work. Thereafter it would, we considered, be reasonable to continue to try the effect of treatment of a number of cases of Ménière's disease with less frequent attacks as out-patients.

*Methods.*—The patients were allowed either ordinary ward diet, or were given a "low salt" diet, i.e. an ordinary diet from which salt had been excluded in the cooking and to which no table salt was added. The patients were intelligent and co-operative and made the effort to eat the same volume of food each day at the same time of day. This was necessary since in these preliminary experiments food sampling was carried out only four times for each patient, twice on normal diet and twice on the "low salt" diet. As a first approximation this was thought to be sufficient as it was hoped by various other means to effect changes in body balance and content of sodium and potassium far greater in extent than occur with daily fluctuations. The various supplements and drugs used on the first 2 patients (Cases I and II) are given in Tables IV and V. The treatment was continuous in each patient, i.e. the dietary periods followed each other without a break for some thirty days. Both the patients, whose balance data are given in Tables IV and V, were women of small stature and were not "big eaters".

TABLE IV.—CASE I

| Dietary period | Cumulative balance to end of period Na mEq. | Cumulative balance to end of period K mEq. | Total cation gain or deficit (from arbitrary zero) mEq. |
|---|---|---|---|
| (1) 6 days: average mixed diet {85 mEq. Na, 48 mEq. K | 0 | 0 | 0 |
| (2) 4 days: ordinary diet + supplement of 160 mEq. K+ | −128 | +257 | +129 |
| (3) 4 days: Low Na diet + supplement of 160 mEq. K+ (48 mEq. Na) | −285 | +396 | +111 |
| (4) 3 days: low Na diet + Diamox + 160 mEq. K+ | −450 | +434 | − 16 |
| (5) 4 days: ordinary diet | −598 | +420 | −178 |
| (6) 5 days: ordinary diet + 85 mEq. Na+ (as NaCl) | −423 | +418 | − 5 |
| (7) 2 days: ordinary diet + 85 mEq. Na+ (as NaCl) + 30 mEq. Na+ (as citrate) | −396 | +428 | + 32 |
| (8) 8 days: ordinary diet + 85 mEq. Na+ (as NaCl) + 30 mEq. Na+ (as citrate) + 2 mg. DOCA. I.M. daily | −131 | +468 | +337 |

The potassium supplement was given in two- to three-hourly doses throughout the waking day. It consisted of a solution of KCl, $KH_2PO_4$, $K_2HPO_4$, $KHCO_3$; the $KHCO_3$ (100 mEq. K) first being nearly neutralized with L-glutamic acid. 25 grams glucose was incorporated in the daily dose volume. The idea of using glutamic acid as a "K+-carrier" and glucose to prevent oxidation of the glutamic acid was derived from the work described by Krebs *et al.* (1951). This mixture has proved to be acceptable and palatable by all patients who have been given it. The figures in Tables IV and V and previous experience, suggest that the potassium is in a form that is absorbed and retained to a greater extent than would be the case with KCl alone. "Low Na" diet. No salt added during cooking or at table. Diamox 125 mg. at 6 a.m. and 125 mg. at 12 noon on each day of administration.

Urine was collected in twenty-four-hour periods throughout the entire experiment and analysed for sodium and potassium content by flame photometry. The start of a dietary period was timed to coincide with the start of a new twenty-four-hour urine collection period.

Food was collected for an entire day, on each sampling occasion, by the method of

TABLE V.—CASE II

| Dietary period | Cumulative balance to end of period Na mEq. | Cumulative balance to end of period K mEq. | Total cation gain or deficit (from arbitrary zero) mEq. | Plasma values mEq./l. | Body weight (kilos) |
|---|---|---|---|---|---|
| (1) 4 days: average mixed ward diet. (75 mEq. Na) (48 mEq. K) | 0 | 0 | 0 | Na−138 K−3·85 | |
| (2) 2 days: average diet + 85 mEq. Na (as NaCl) | +135 | −14 | +121 | | |
| (3) 6 days: ordinary diet + 85 mEq. NaCl + 30 mEq. Na (as citrate) + 2 mg. DOCA IM daily | +165 | −87 | + 78 | Na−143 K−3·7 Na−143 K−3·55 | |
| (4) 4 days: ordinary diet + 85 mEq. NaCl + 30 mEq. Na (as citrate) + 2 mg. DOCA IM daily + (Resonium-A) sodium cycle resin 15 g. 4 times a day: calculated as 100 mEq. Na exchanged | +354 | −521 | −167 | Na−143 K−3·28 | Wt. incr. =2·7 kg. |
| (5) 6 days: ordinary diet only | −406 | −338 | −744 | Na−143 K−3·93 | |
| (6) 2 days: ordinary diet + supplement of 160 mEq. K | −547 | −232 | −779 | | |
| (7) 2 days: low Na diet + 160 mEq. K (48 mEq. Na) | −602 | −170 | −772 | | |
| (8) 2 days: low Na diet + 160 mEq. K + Diamox | −691 | −217 | −908 | | |
| (9) 1 day: low Na diet + 160 mEq. K + (Katonium) K cycle resin 15 grams 3 times/day: calculated as 50 mEq. K exchanged | −749 | −159 | −908 | | |
| (10) 3 days: low Na diet + 160 mEq. K + 50 mEq. exchanged from resin + Diamox | −843 | +207 | −636 | Na−138 K−4·00 | |

measuring what the patient ate of each dish and placing an equal quantity in the receiver for homogenization. The total day's food and drink were homogenized to a fluid smooth enough to be pipetted, and quadruplicate samples taken off into weighed evaporating basins. The total homogenate was also weighed. In the first trials the samples were taken to dryness, under an infra-red lamp, carefully ashed with sulphuric or nitric acid and the digest suitably diluted for the estimation of sodium and potassium by flame photometry. Later food analyses were done by wet digestion of the samples with sulphuric or nitric acid since this method gave more consistent results in addition and recovery experiments.

Loss of sodium and potassium in the fæces was neglected except for the resin periods in Case II. The loss of ions by this route was calculated from data on average *in vivo* exchange rates given by other workers.[1]

*Results.*—The results are given in Tables IV and V and show the cumulative balance for each ion by the end of each dietary period as well as the overall balance for the whole period. After a short preliminary period on ordinary ward diet the assumption was made that a state of ion balance had been achieved. This is a purely arbitrary assumption and, as pointed out later, may well not have been true.

## DISCUSSION

*Table IV.*—The continued loss of sodium during period 5 would seem to require explanation; it is possibly due to the form in which the potassium was administered. If the administered potassium were displacing cellular sodium—and indeed no evidence of dehydration appeared—the return to ordinary diet and normal sodium intake would, in the first place, not influence extracellular sodium—and expansion of extracellular fluid volume did not, in fact, occur until period 8 when a definite increase in weight took place. However, the avidity which this patient's tissues had for $K^+$ both in uptake and retention would suggest that the arbitrary zero set at the end of the six days' mixed diet might have been a state of

[1]These data were kindly provided by the resin manufacturers, Messrs. Bayer Products Ltd., Kingston-on-Thames, Surrey.

chronic negative potassium and positive sodium balance. The figures recorded up to the end of period 7 would then be a record of fluctuations towards a more normal state of balance.

Even with these assumptions the failure to excrete potassium while retaining sodium under the influence of DOCA is still not clearly explained. It should be emphasized that the patient (Case I) became progressively better (subjectively) on this treatment and stated she had never felt so fit as at the end of the course, and has remained well since.

*Table V.*—As in Table IV care has been taken to underestimate the extent of the changes. A definite sodium loading was achieved followed by a significant sodium deficit. During the DOCA period a large diuresis of potassium occurred which was not made good and converted to a positive balance until the last periods when potassium cycle resin was used.

There was a considerable rebound diuresis of sodium after stopping DOCA administration, but the continued sodium loss in the later periods would appear to have come from intracellular sources since no evidence of dehydration appeared. No clinical change was noted until the last period when the patient volunteered to having felt better than for some time past, and appeared to become more confident in attitude.

The two experiments taken together demonstrate large, fairly acute fluctuation of body electrolyte content, with both sodium and potassium in excess and in deficit, without the precipitation of any attack of vertigo; further, it would seem reasonable to conclude that if it required these severe measures to enforce significant changes in body balance and content of the electrolytes it is unlikely that the more gentle treatment of low sodium diet or a moderate potassium chloride supplement would influence homeostasis for any considerable period of time.

One suggestion, however, remains; as mentioned before, the patient whose data are recorded in Table IV might have been in chronic negative potassium balance. The difficulty in the second experiment (Table V) of obtaining a "good" response to DOCA alone, either in sodium retention or potassium excretion, again suggests a refractoriness which may perhaps have originated in a relative sodium excess and potassium deficit in the organism.

Our next investigations were designed in a fashion similar to those of Perlman *et al.* (1953). We started by assuming that the currently accepted theory of œdema of the membranous labyrinth was correct. If salt and water restriction did, in fact, produce improvement and prevent endolymphatic œdema, the reverse treatment—that of salt and water loading—might perhaps, though not necessarily, produce the opposite effect. The occurrence of spontaneous remission in Ménière's disease makes it very difficult to prove that a particular line of treatment has had an effect on causation, if improvement results. We therefore tried to produce the opposite situation, an increase in the number of attacks being experienced by the patients; in fact, however, during the periods of acute salt loading no attack occurred at all. The patients who were the subjects of the salt-loading treatment were clinically all cases of active Ménière's disease.

3 patients, Cases III, IV and V, after a short period of normal diet with normal allowance of table salt, were placed directly on a regime of added dietetic salt and DOCA administered intramuscularly. All drugs were stopped at least three days before the start of this treatment period. For the first two days 3 grams sodium chloride was given in divided doses, and thereafter for six days, 5 grams sodium chloride in addition to normal intake. 2 mg. DOCA was administered each day for eight days. The effects of this regime were estimated by the clinical response, by audiometry, by change in body weight and by plasma electrolyte values. The weight changes recorded were increases during the salt-loading period of 1·75, 1·5 and 0·66 kg. and were accompanied by significant changes in the expected directions in the concentrations of plasma sodium, chloride and, in one case, potassium.

One patient (Case III) showed no change throughout in his audiogram, and subjectively was improved. One patient (Case IV) showed continuous improvement in the audiograms of both ears and also continuous subjective improvement. The third patient (Case V) gave variable responses in the audiograms and made complaint of headaches and of a feeling of pressure in the temporal regions during the DOCA period, but he thought his symptoms were quite different from those of an impending attack of Ménière's disease.

The next 3 patients (Cases VI, VII and VIII) were given similar treatment except for a preparatory period of three days' treatment with Mictine (aminometradine) a non-mercurial diuretic which aids elimination of sodium in the urine. The effect of the drug was maintained for three days by starting with a low dosage and increasing the dose daily. By this means an initial drop in body weight was obtained, in one case without change in plasma electrolyte concentrations, and in the others with significant increases in plasma concentrations of $Na^+$, $K^+$ and $HCO_3$. The subsequent salt-loading regime, similar to that used for the first three cases, produced body weight increases of 2·56, 2·7 and 2·95 kg. respectively. In 1 case (VI), there were further considerable changes in plasma electrolyte concentrations, sodium, chloride and bicarbonate continuing to increase, while potassium concentration fell. In the other cases no additional concentration changes occurred.

Apart from a subjective feeling of improvement, no symptoms of note occurred, nor did the audiograms record any significant changes.

Table VI gives a summary of the data of this treatment.

TABLE VI

| Patient | Maximum change in body weight (kg.) | Change in plasma values during DOCA period (mEq./l.) Na | K |
|---|---|---|---|
| III | 1·75 | +3·0 | No change |
| IV | +1·5 | No change | |
| V | +0·66 | +9·0 | −0·9 |
| VI | +2·56 | +10·0 | −1·3 |
| VII | +2·70 | No change | −0·5 |
| VIII | +2·95 | No change | −0·7 |

Normal plasma values: sodium 142 ± 1·5 mEq./l/
potassium 5 ± 0·25 mEq./l.
(the ± error being 3 × S.D.)

The interpretation of these results must take into account the fact that definite increases in extracellular fluid were obtained, and in some cases a greater sodium than water retention. If a low salt intake is capable of preventing attacks of Ménière's disease in certain cases it may not follow that a high salt intake must precipitate such attacks. What we have shown, however, is that short-term treatment with high salt intake and with DOCA led to subjective improvement, so considerable in fact that one patient pleaded for a second course of treatment. The regime we have described led to more acute and extensive changes in body fluids and electrolytes than is likely to occur during any normal dietary intake. The kidneys and adrenal glands of patients with Ménière's disease may be presumed to function normally, and the usual physiological mechanisms are at work adjusting turnover and output of salt to the needs of the organism given a particular level of intake. Perhaps it should not have been expected that any increase in frequency and severity of attacks would occur in patients receiving the high salt intake, but neither should we have found such unanimous well-being and general improvement.

After a suitable interval of time, to allow readjustment of electrolyte balance to occur, i.e. upwards of one month from the end of the salt-loading regime, these same patients were given a further short period of treatment. On this occasion potassium loading was aimed at and a mixture of potassium chloride and phosphates was administered as a supplement to the diet, the extra potassium being taken in divided doses throughout the day to a total of 60 mEq. per day. On the third day the load was increased to 120 mEq., the additional potassium being exhibited as glutamate. On the fifth to seventh days 160 mEq. $K^+$ was administered, the extra potassium again being in the form of glutamate. At the end of a week on this regime, although none of the patients felt or showed audiometrically that any change, either improvement or regression, had taken place in hearing or tinnitus, all the patients volunteered the information that they felt less tired and more able to cope with the day's work. A positive, more confident attitude of mind resulting, at least in part, from the feeling of well-being, was a notable feature in every case.

However, the effect of potassium loading in the last three days may have been partly obscured by the amount of glutamate given, for, in the dosage used, a stimulatory effect on the adrenal medulla might have been evoked (Weil-Malherbe, 1950). Change in body weight was not great, but with one exception the trend was towards an increase. (The exception was almost certainly due to extra heavy muscular effort.)

There were few significant changes in plasma concentrations, but the changes that did occur were in the direction of increased concentrations of both sodium and potassium, except in one instance where there was a small drop in sodium concentration.

We have no data to prove potassium retention and an increase in total body potassium by our treatment; our regime, however, was not so dissimilar to that used by other workers, that the effects on aldosterone secretion could be considered different. If, in our patients, an increased secretion of aldosterone occurred, then we would expect a preliminary excretion of sodium in response to the potassium loading and thereafter a sodium retention phase to be in operation by the end of the week's treatment. By this means, an increase, probably temporary, in total body content of sodium and potassium would be achieved, and this possibility is reflected in the tendency of the plasma values of both sodium and potassium to increase, with, as mentioned before, one exception.

The intention with sodium chloride and DOCA administration was to achieve a salt loading and expansion of the extracellular fluid of the organism, in contrast to the fall of extracellular fluid intended by the salt-restriction regime. There would seem little doubt

that we did in fact achieve salt retention and expansion of the extracellular space, but it may be argued that we may have defeated our own purpose by using DOCA. Administration of this steroid expands the extracellular space at the expense of intracellular water (Gaudino and Levitt, 1949; and Luft *et al.*, 1954), and until there is conclusive proof that our suggestion (Naftalin and Harrison, 1958) that the endolymph is extracellular in origin is correct, the interpretation of the experiments reported here must remain open. If the endolymph is of intracellular origin after all, then this DOCA regime may be a means of reducing endolymphatic œdema.

In the patient suffering from an attack of Ménière's disease, if the adrenal cortical glands play any part at all, it will be by the increased secretion of the natural hormones, hydrocortisone and aldosterone, not of DOCA. The effect of cortisone on intra- or extracellular fluids is the opposite to that of DOCA. Administration of cortisone increases intracellular water and decreases extracellular water, while the effects of aldosterone—potassium release and sodium retention—would tend to oppose the action of cortisone in these respects. We have some direct evidence from the work of Talbott and Brown (1940) that changes in electrolyte concentrations occur during an attack of Ménière's disease. They found that serum $K^+$ was raised and Na concentration lowered during an attack. This could mean a shift of water and potassium from the intracellular fluid to the extracellular fluid, an aldosterone, or DOCA-like effect, or a movement of sodium and water intracellularly, the sodium shift being greater than the water, a result which could be due to cortisone.

## CASES

*Case I.*—Miss E. S., aged 43, first seen March 1950 complaining of frequent attacks of rotational vertigo occurring intermittently for seven years. Buzzing tinnitus left ear and deafness on that side. Vomiting with the attacks. The symptoms continued, though less severely, with sedation, and the patient returned in April 1956 on account of very frequent severe attacks, three or four weekly, and loud tinnitus. Caloric test showed some left-sided deficiency.

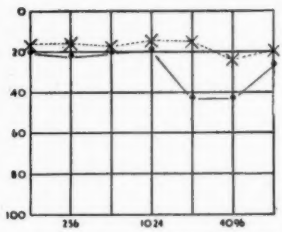
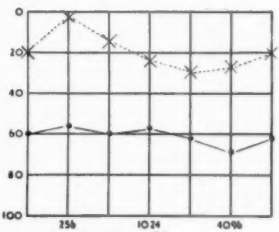



FIG. 1 (*Case I*).—23.3.50.




o—o Left ear. x.....x Right ear

FIG. 2 (*Case I*).—19.4.56.

Difference limen:

| | Right | | Left | |
|---|---|---|---|---|
| | + 10 Db. | + 40 Db. | + 10 Db. | + 25 Db. |
| 125 | 0·25 | 0·25 | 0·0 | 0·0 |
| 250 | 1·0 | 0·5 | 0·25 | 0·0 |
| 500 | 0·0 | 0·0 | 0·75 | 0·0 |
| 1,000 | 1·25 | 0·25 | 0·0 | 0·0 |
| 2,000 | 1·25 | 0·75 | 0·25 | 0·25 |
| 4,000 | 1·25 | 1·00 | 0·75 | 0·5 |
| 8,000 | 2·0 | 1·25 | 0·5 | 0·25 |

The patient was referred to Dr. C. S. Hallpike's clinic for confirmation of the diagnosis.

Figs. 3 and 4: Loudness balance tests revealed complete recruitment of loudness of the left ear at 512 and incomplete at 1,024 and 2,048, probably owing to the little deafness which was present in the right ear. Investigation of the deafness on the right side by special tests showed that loudness recruitment was present on that side also. The caloric and loudness balance tests showed the patient to be suffering from bilateral Ménière's disease, but it was felt inadvisable to carry out destructive surgery.

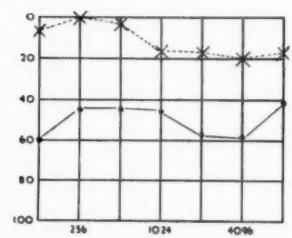



FIG. 3 (*Case I*).—18.12.56.

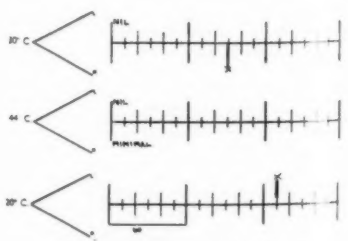


FIG. 4. (*Case I*).—18.12.56.

*Case II.*—Mrs. E. B., aged 56, first seen 21.6.56, with attacks of rotational vertigo and vomiting of some months' duration, attacks usually lasting two hours. Deafness and buzzing tinnitus left ear for a year.

The ears, nose and throat were healthy on examination.

*On examination.*—

| Hearing | Right | Left | |
|---|---|---|---|
| Rinne | pos. | pos. | X-ray of sinuses—clear. |
| Weber | ← | | 512 W.R. negative |
| A.B.C. | ↓ 7 sec. | ↓ | |

Active corneals.
No spontaneous nystagmus.
No positional nystagmus.
Steady on Romberg's test.

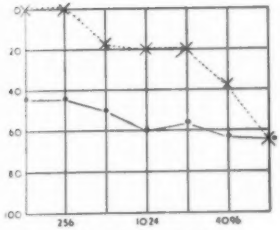


FIG. 5 (*Case II*).

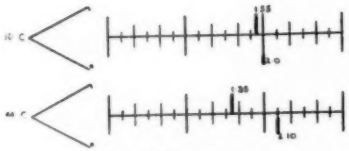


FIG. 6 (*Case II*).—L.C.

In April 1957 the patient's response to medical treatment with sedation and vasodilators was not very satisfactory and she was admitted as she was having frequent attacks, two or three times per week, for biochemical investigation.

During the course of the investigation repeated audiograms were carried out and showed little variation of note in the hearing.

*Case III.*—Mr. J. A., aged 42, first seen 10.10.57, with deafness on the left side and attacks of rotational vertigo with vomiting, commencing in August 1957. Ringing tinnitus in the left ear.

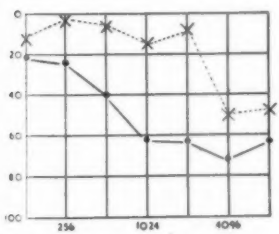


FIG. 7 (*Case III*).—10.10.57.

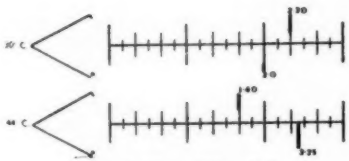


FIG. 8 (*Case III*).—R.P.

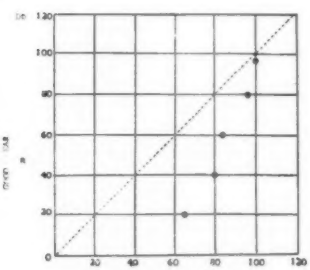


FIG. 9 (*Case III*).

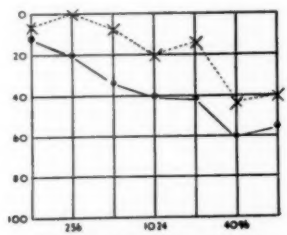


FIG. 10 (*Case III*).—12.1.58.

No history of head injury. Ears, nose and throat healthy.
Biochemical investigations carried out 13.11.57 to 20.11.57.

*Case IV.*—Miss J. B., aged 41, first seen 31.5.56, complaining of attacks of rotational vertigo and deafness in both ears. Marked tinnitus. Ears, nose and throat healthy.

*On examination.—*

| Hearing | Right | Left | |
|---|---|---|---|
| Rinne | pos. | pos. | 512 |
| A.B.C. | marked fall | | |

Patient continued to have dizzy attacks in spite of treatment and the hearing showed considerable variation (Figs. 13, 14, 15 and 16).
Biochemical investigation carried out 30.12.57 to 11.1.58.

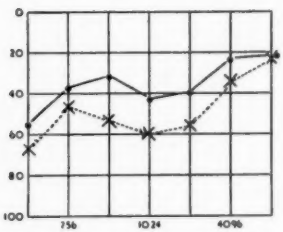



FIG. 11 (*Case IV*).—31.5.56.

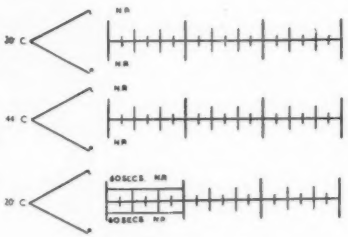



FIG. 12 (*Case IV*).

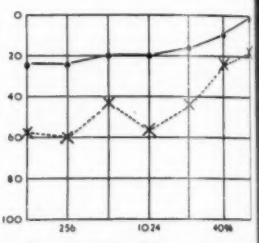



FIG 13 (*Case IV*).—11.8.56.

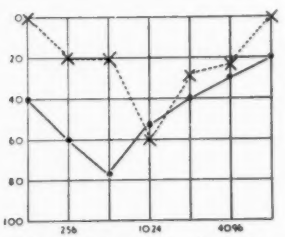



FIG. 14 (*Case IV*).—13.12.56.

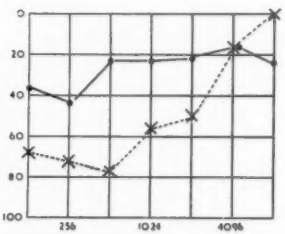



FIG. 15 (*Case IV*).—6.6.57.

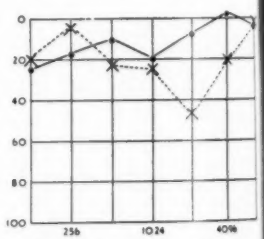



FIG. 16 (*Case IV*).—28.12.57.

*Case V.*—Mr. J. H., aged 47, first seen 5.9.57, complaining of constant ringing in the left ear since June 1957 with attacks of severe rotational vertigo and vomiting. He had had similar attacks two years previously. Some deafness and distortion of hearing on the left side. Ears, nose and throat healthy.

*On examination.—*

| Hearing | Right | Left | |
|---|---|---|---|
| Rinne | pos. | pos. | 512 |
| Weber | ← | | |
| A.B.C. | marked fall | | |

Biochemical investigations carried out from 22.11.57 to 4.12.57. When seen on 13.2.58 patient had been well up to a month before, but since then had had further attacks of dizziness and tinnitus.

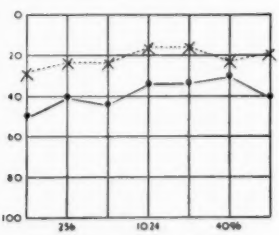



FIG. (17 *Case V*).

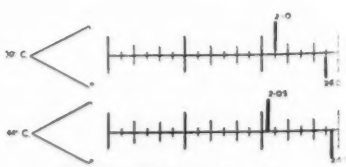



FIG. 18 (*Case V*).—R.C.P.

*Case VI.*—Mr. R. B., aged 63, first seen 21.11.57, having had attacks of rotational vertigo and progressive deafness on the right side since May 1957. No tinnitus. No history of head injury. Ears, nose and throat healthy.

*On examination.*—

| Hearing | Right | Left | |
|---|---|---|---|
| Rinne | pos. | pos. | 512 |
| Weber | → | | |
| A.B.C. | 8 sec. | ↓ | |

X-ray of sinuses—some mucosal thickening of the antra, particularly right.

D.A.P. and W.O.—mucopus from the right side.

X-ray of petrous bones—appearances are within the limits of normal.

Biochemical investigations carried out 14.1.58 to 25.1.58.

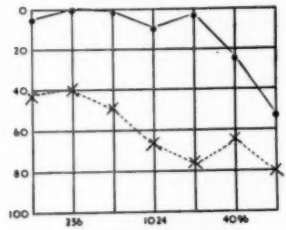



FIG. 19 (*Case VI*).

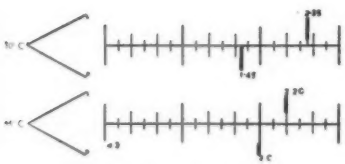


FIG. 20 (*Case VI*).—R.C.P.

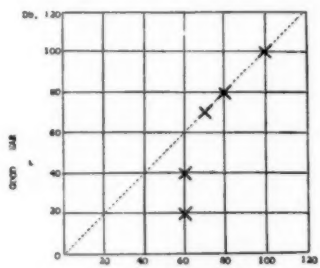



FIG. 21 (*Case VI*).

*Case VII.*—Mr. J. T., aged 62, first seen 14.11.57. He had had vertiginous attacks with clockwise rotational vertigo for four years. The attacks had never occurred in bed. Duration two hours. Progressive deafness in the left ear with a constant buzzing and hissing tinnitus on the left side. Ears, nose and throat healthy.

*On examination.*—

| Hearing | Right | Left | |
|---|---|---|---|
| Rinne | pos. | pos. | 512 |
| Weber | ← | | |
| A.B.C. | ↓ | 10 sec. | |

Very little hearing in the left ear with masking of the right ear.

6.2.58: Some improvement with nicotinic acid, but still having attacks. Biochemical investigations carried out 6.2.58 to 27.2.58.

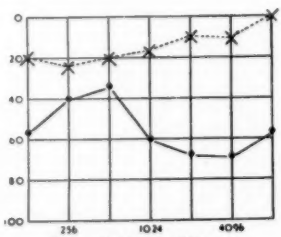



FIG. 22 (*Case VII*).

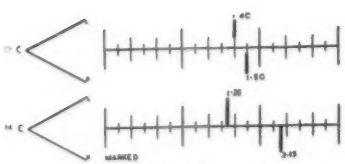


FIG. 23 (*Case VII*).—L.C.

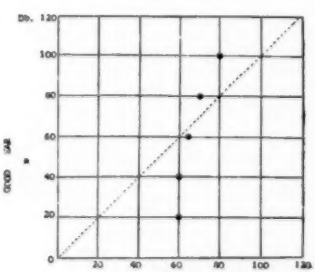



FIG. 24 (*Case VII*).

*Case VIII.*—Mr. M. C., aged 28. First seen on 28.10.54, complaining of vertigo and deafness in the left ear of four to five years' duration, with buzzing tinnitus on the left side. Ears, nose and throat healthy.

*On examination.*—

| Hearing | Right | Left | |
|---|---|---|---|
| Rinne | pos. | pos. | } 512 |
| Weber | ← | | |
| A.B.C. | ↓ 8 sec. | ↓ | |

X-ray of sinuses showed opacity of the right antrum due to thick pus shown on washout. Infection cleared with repeated washouts. The hearing loss on the left side remained fairly constant, but there was some fluctuation in the hearing on the right side. The condition thus appeared to be bilateral.

In January 1958 the patient was seen by Mr. Neville Young of Manchester, who confirmed the diagnosis of Ménière's disease.

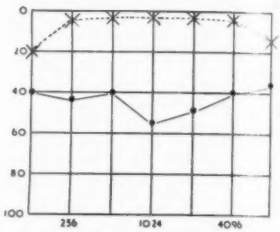



FIG. 25 (*Case VIII*).—28.10.54.

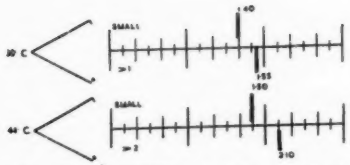


FIG. 26 (*Case VIII*).—L.C.P.—28.10.54.

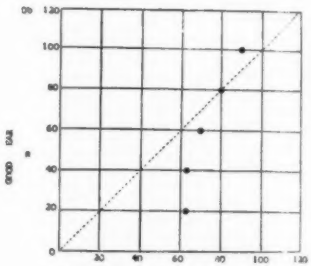


FIG. 27 (*Case VIII*).

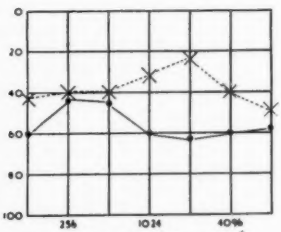



FIG. 28 (*Case VIII*).—5.2.58.

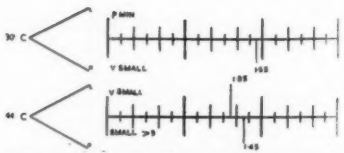


FIG. 29 (*Case VIII*).—? L.C.P.—5.2.58.

## CONCLUSION

Considerable variations in the sodium and potassium balances in the body fluids were obtained by restriction and addition of these substances in the diet of typical cases of Ménière's disease. No effect was noted in the 8 cases investigated other than a notable improvement in their general condition on either sodium or potassium loading regime, leading one to suspect that patients suffering from Ménière's disease develop a chronic state of total cation deficiency, and it may be immaterial which cation, sodium or potassium, is replaced in the first instance.

It seems to us that these problems can only be resolved by a systematic approach, estimating urinary aldosterone and 17-hydroxycorticosteroids in a series of patients with Ménière's disease in remission and awaiting the opportunity of assaying these hormones during and following an acute attack. The question of chronic $K^+$ deficiency in these patients should be simultaneously investigated by full balance procedures and if necessary by twenty-four-hour exchangeable $^{42}K$.

REFERENCES

CITRON, L., EXLEY, D., and HALLPIKE, C. S. (1956) *Brit. med. Bull.*, **12**, 101.
CROWE, S. J. (1938) *Medicine, Baltimore*, **17**, 1.
DEDERDING, D. (1929) *Acta. Otolaryng., Stockh.*, Suppl. 10–11.
FURSTENBERG, A. C. (1936) *Trans. Pacif. Cst oto-ophthal. Soc.*, **21**, 150.
——, LASHMET, F. H., and LATHROP, F. (1934) *Ann. Otol. Rhin. Laryng.*, **43**, 1035.
GAMBLE, J. L. (1951) Companionship of Water and Electrolytes in the Organisation of Body Fluids. Stanford and London.
GAUDINO, M., and LEVITT, M. F. (1949) *J. clin. Invest.*, **28**, 1487.
HARRISON, M. S. (1956) *J. Laryng.*, **70**, 680.
KREBS, H. A., EGGLESTON, L. V., and TERNER, C. (1951) *Biochem. J.*, **48**, 530.
LEWIS, R. S. (1956) *J. Laryng.*, **70**, 673.
LUFT, R., SJORGREN, B., IKKOS, D., LJONGREN, H., and TARNKOSKI (1954) *Recent Progr. Hormone Res.*, **10**, 425.
MYGIND, S. H. (1943) *Ugeskr. Laeg.*, **105**, 567.
—— and DEDERDING, D. (1938) *Ann. Otol. Rhin. Laryng.*, **47**, 55, 768.
NAFTALIN, L., and HARRISON, M. S. (1958) *J. Laryng.*, **72**, 118.
PERLMAN, H. B., GOLDINGER, J. M., and CALES, J. O. (1953) *Laryngoscope, St. Louis*, **63**, 640.
TALBOTT, J. H., and BROWN, M. R. (1940) *J. Amer. med. Ass.*, **114**, 125.
WALSH, M. N., and ADSON, A. W. (1940) *J. Amer. med. Ass.*, **114**, 130.
WEIL-MALHERBE, H. (1950) *Physiol. Rev.*, **30**, 549.


**Dr. G. D. McDowall** (Edinburgh): *The Medical Treatment of Ménière's Disease: A Long-term Survey of* 116 *Cases*

Whilst we may be on the threshold of a better understanding of the composition and circulation of the labyrinthine fluids, these advances in knowledge, with improved methods of investigation, have made little impact on the medical treatment of the disease within the past decade. "The treatment of Ménière's disease is largely symptomatic" (*British Medical Journal*, 1957). Despite the implied limitation and the air of pessimism which has surrounded the treatment of the disease the statement has been frequently repeated that by one means or another, the majority of patients can be relieved of the constant fear of an impending attack of vertigo.

It seems relevant first to assess, as accurately as possible, the results of medical treatment before considering the possibilities and results of surgery with particular reference to ultrasonic therapy, which, though conservative in its aim to preserve hearing, is radical in its application to the vertigo-producing labyrinth. The fact that hearing may be retained may tend to justify the earlier use of this method without a prolonged trial of medical measures which have in the past been advised before ablation of the labyrinth, particularly in those patients whose economic circumstances demand early relief from vertigo.

The difficulties of assessing the value of treatment in this disorder are well known. The natural remissions of the disease, with or without treatment, are variable in duration. Their average duration in McNally's series of cases was four years (McNally *et al.*, 1949), and for this reason he considered that a minimum period of five years, free from symptoms, is necessary before a cure could be determined. Other reports are based on shorter periods of observation, usually two years, which may be adequate to determine the result of treatment including spontaneous remissions.

*Material.*—This brief communication aims to evaluate the results of medical treatment over a minimum period of five years. The patients in this series were all seen and examined for the first time prior to March 1953. Examination of the records of the Ear, Nose and Throat Department, in Dr. Simson Hall's charge at the Edinburgh Royal Infirmary, revealed that in the years between 1946 and March 1953 there were 174 patients whose diagnosis of Ménière's disease could be confirmed and who had received adequate treatment under the supervision of the department. Of this number 20 cases were treated by surgery and are not included in this survey. The remaining 154 patients were given the opportunity of attending at the out-patient department by appointment or of replying to a questionnaire. 116 patients were seen and personally examined or replied to the questionnaire. 31 patients were untraced and 7 deaths were recorded. The figure of 116 cases contacted out of the total 154, or 75% of the series, is not large when compared with 94% in the survey made by Goodman (1957) at Oxford. The geographical area from which the present series is drawn is a large one and with the longer follow-up period accounts for the lower response.

Many of the patients have attended the out-patient department regularly for several years, and, as a group, are punctilious in keeping appointments. In this they have been encouraged because it has been found that regular attendance at a clinic, an unhurried consultation, and, if necessary, a variation of treatment, have tided many patients over a period of frequently recurring attacks without loss of self-confidence.

*Aetiology.*—Many otologists have maintained that mental disturbances are the result and not the cause of Ménière's disease and there is no doubt that uncontrolled vertigo does

UNIVERSITY OF MICHIGAN LIBRARIES

produce mental disturbances. On the other hand there is evidence that autonomic dysfunction is, at least, the trigger mechanism of Ménière's disease and it has been shown that sympathetic-parasympathetic imbalance may be caused by emotional stress. In this series many cases could be cited where the disease has been associated with a state of anxiety, where a prolonged remission has occurred when the period of stress has ended or the individual became adjusted to environment.

There are 70 males and 46 females in this series, an unusual preponderance of males. The age of the patients at the onset of the disease bears out previous contentions that the majority of patients have their first attack before the age of 50. 68% of cases occurred between the ages of 21 and 50. An analysis in decades illustrates the age distribution:

TABLE I.—AGE AT ONSET OF FIRST SYMPTOM (YEARS)

| 21–30 | 31–40 | 41–50 | 51–60 | 61–70 |
|---|---|---|---|---|
| 10 | 31 | 38 | 29 | 8 |

If mental stress and strain are regarded as significant factors in the production of autonomic imbalance which initiates the attacks of Ménière's disease, then this age incidence, with its high rate during the years of increasing responsibility, might be of significance. There must, however, be some intrinsic factor also, otherwise might we not expect a high incidence of the disease in the medical profession in the ranks of time-expired registrars and underpaid consultants?

*Diagnosis.*—The diagnosis of Ménière's disease is not always easy, particularly the early case. Careful scrutiny of the files and case histories showed that 19% of the cases could be excluded and required to be recategorized. A careful case history and full clinical examinations are essential in the investigation. The recruitment test is now part of the routine examination but is recorded in only 31 patients in all of whom the phenomenon was present. The differential caloric tests were recorded in 106 patients and an abnormal response noted in 86% of cases. The patterns found are shown in Table II.

Table III gives the results obtained by Hallpike (1956) in the examination of several hundreds of subjects.

| TABLE II | % |
|---|---|
| Canal paresis | 51 |
| Directional preponderance | 26 |
| Combined lesion | 9 |
| Normal | 14 |

| TABLE III | % |
|---|---|
| Canal paresis | 49 |
| Directional preponderance | 21 |
| Combined lesion | 18 |
| Normal | 12 |

There is thus, apart from the incidence of combined lesion, no significant difference between these figures, and, as he has observed, the pattern varies in one individual in the course of the disorder.

The histamine skin test was recorded in 103 patients, positive in 31, negative in 56 and variable in 16. According to Atkinson (1946) this test divides Ménière patients into two groups, the histamine-positive or smaller group and the histamine-negative group. In a controlled investigation at the London Hospital, Haggie (1951) showed that the test did not differentiate normal individuals from patients with Ménière's disease. Williams (1946) also considered the test inaccurate. Experience in this investigation showed that patients gave different reactions on different occasions and its use as an indication for histamine desensitization or nicotinic acid treatment was unreliable.

*Symptomatology.*—The classical triad of symptoms was present in 82 patients and in the remaining 34 tinnitus was absent or slight. 34 patients complained of deafness, in some cases for several years before the onset of vertigo. In the majority of cases, however, vertigo was the presenting symptom. 3 cases associated the onset of the disease with tinnitus. No significant relationship could be established between the original symptom and the age of onset.

Bilateral deafness was noted in 38 patients, almost 33%—19 of whom were over 50 years of age and 19 under that age. The disease was bilateral in 9 patients. Distortion of hearing was not a common complaint, but headache related to the occipital area or a sensation of fullness and tightness extending from the mastoid area over the side of the head was frequently described by patients.

*Treatment.*—Sedation, notably with phenobarbitone, is a well-tried method of dealing with this disease and it has undoubtedly a necessary place in the treatment of the acute attack. For long-term use, however, it is an inadequate form of treatment, which, like the tranquillizers, relieves the patient by dulling the perception and overcoming environmental factors. It is frequently used in combination with dietary and anti-retentional regimes.

The principal methods of treatment in this series have been those advocated by Atkinson (1946) whose methods have since been elaborated and advanced by the work of Hilger and

Goltz (1951). Histamine, except for a few early cases treated by intravenous infusion, has been given by graduated subcutaneous injections and maintained by injection of more concentrated solution at weekly or twice weekly intervals, sometimes for prolonged periods. Others have had repeated courses of histamine when a recurrence of vertigo occurred.

Nicotinic acid therapy has been given as an initial intravenous course by daily injection and maintained by intramuscular and/or oral administration.

To both of these preparations riboflavin has been added, given parenterally and orally. A substantial number of patients received treatment with histamine and nicotinic acid at different times, one or other drug having failed to produce relief, and are assessed as a separate group. A sixth group is formed by those who had combinations of treatment from which no specific method could be separated.

As in most surveys of this disease the results of treatment are evaluated on the success or otherwise achieved in relieving vertigo, which is the symptom causing most distress, leading to economic difficulty or to premature retirement. Whilst deafness and tinnitus add to the patient's difficulties, they are seldom of first importance.

TABLE IV.—RESULTS OF TREATMENT

Relief for five years (according to the suggestion of McNally)

| Treatment | No. of cases | Relieved |
|---|---|---|
| Histamine .. .. .. | 15 | 8 |
| Nicotinic acid .. .. .. | 45 | 23 |
| Histamine and nicotinic acid .. | 18 | 4 |
| Histamine and riboflavin .. | 9 | 1 |
| Nicotinic acid and riboflavin .. | 10 | 2 |
| Combined methods .. .. | 19 | 1 |
| Total | 116 | 39 (34%) |

TABLE V.—RELAPSED AND UNSUCCESSFUL CASES

| Treatment | No. of cases | Relief for 2 years | Temporary relief | No relief |
|---|---|---|---|---|
| Histamine .. .. .. | 7 | 3 | 0 | 4 |
| Nicotinic acid .. .. | 22 | 11 | 7 | 4 |
| Histamine and nicotinic acid | 14 | 2 | 4 | 8 |
| Histamine and riboflavin .. | 8 | 2 | 2 | 4 |
| Nicotinic acid and riboflavin | 8 | 2 | 1 | 5 |
| Combined methods.. .. | 18 | 5 | 3 | 10 |
| Total | 77 | 25 (21%) | 17 (15%) | 35 (30%) |

After all forms of treatment, therefore, 39 cases or 34% had no vertigo for five years or longer. Of the long-term unsuccessful cases 25 or 21% had no vertigo for two years, 17 cases or 15% had temporary relief, 35 cases or 30% had no satisfactory relief.

*Hearing.*—It was not possible to perform audiometric tests on all patients reviewed and the following figures are subjective:

| | |
|---|---|
| Hearing improved .. .. .. | 10 patients |
| Hearing unchanged or varies .. | 59 patients |
| Hearing deteriorated .. .. | 47 patients |

*Tinnitus.*—No attempt was made to assess the effect of treatment on tinnitus but only 3 patients complained of severe tinnitus and it was bilateral in 15 patients.

It has already been stated that many of these patients have been regular in their attendance at the out-patient clinic for the past eight to ten years and some have had prolonged treatment, particularly those treated with nicotinic acid, of whom 30, or two-thirds, continue to have intermittent therapy. This is, perhaps, responsible for the improved result in the five-year group compared with McNally *et al.* (1949) in whose series nicotinic acid did not produce a lasting cure in any of the cases. The figures for histamine treatment, however, are in agreement with his observation that histamine is not as effective in producing temporary or symptomatic relief.

Williams (1955) believes that combination of the several methods of treatment is more effective than giving one after another and he considers that the symptoms of Ménière's disease can be alleviated in about 75% of patients. This survey has shown that by the various medical treatments employed, relief of varying duration was obtained by 70% of the patients.

Reports of surgical treatment indicate that this method is required in between 10% and 30% of patients. Whichever figure is accepted there is undoubtedly a substantial number of patients who require relief from vertigo, not at present obtainable by medical means.

A survey of this kind is a heartening experience. Frequent return of failures prevents complacency but leads to pessimism. The cured and grateful are seldom seen.

I should like to express my indebtedness to Dr. Simson Hall for his valued advice and the unrestricted opportunity to make this survey.

REFERENCES

ATKINSON, M. (1946) *Proc. R. Soc. Med.*, **39**, 807.
*Brit. med. J.* (1957) ii, 754.
GOODMAN, W. S. (1957) *J. Laryng.*, **71**, 339.
HAGGIE, M. (1951) *Brit. med. J.*, ii, 1057.
HALLPIKE, C. S. (1956) *J. Laryng.*, **70**, 15.
HILGER, J. A., and GOLTZ, N. F. (1951) *Laryngoscope, St. Louis*, **61**, 695.
MCNALLY, W. J., STUART, E. A., MCKERCHER, D. D., and LOCKHART, H. B. (1949) *Congr. int. Oto-rhino-laryng.*, IV, **1**, 195.
WILLIAMS, H. L. (1946) *Proc. Mayo Clin.*, **21**, 58; (1955) *Arch. Otolaryng., Chicago*, **62**, 573.

**Mr. Thomas J. Wilmot:**

The most significant contribution to the discussion has been the results of Mr. Spencer Harrison's follow-up of his personal sympathectomy cases done seven years ago. These show clearly that sympathectomy has a place to play in the treatment of Ménière's disease. I agree with him that the bilateral case with progressive hearing loss is the one where sympathectomy must be considered.

In ultrasonic treatment of the vestibular symptoms in this condition even if the vestibular symptoms are controlled the progressive lesion in the cochlea is not. This form of treatment does nothing towards controlling the actual pathological mechanism involved. It is, in fact, only a more complicated and expensive method of destroying an organ which should not need to be destroyed at all.

Ménière's disease has an early and often reversible stage and if diagnosis can be made at this stage, the function of both cochlea and vestibule can be restored to normal in many cases. It is insufficiently realized that, for such early diagnosis, time and special equipment are necessary and there are far too few centres in the United Kingdom where these are available. Our attitude of focusing attention upon the advanced case of Ménière's where destructive measures may be necessary has been responsible for this state of affairs.

[In the case of a man of 53 with bilateral cochlear involvement and unilateral vestibular involvement, slides were shown of the audiograms and of the actual electrical nystagmographic recordings of the caloric tests before and after sympathectomy. These illustrated the degree of recovery of both cochlear and vestibular function following bilateral cervical sympathectomy. Complete return of previously absent vestibular function was clearly demonstrated together with definite hearing improvement.]

Obviously stellate block and sympathectomy have a part to play in this condition. We do not know yet how permanent the results of sympathectomy are, but any measure which can conserve or restore function is of value.

**Mr. Charles Smith:**

132 cases of aural vertigo under treatment at St. Thomas's Hospital for more than five years have been reviewed. They include 53 cases of Ménière's disease reported on in 1950 by Kodicek, Taylor and Bateman and the majority are cases collected and summarized by Mr. Kodicek. All were written to and if possible interviewed. 50 letters were unanswered and 37 could not be traced or were discarded as the diagnosis of Ménière's disease was not established. 45 were contacted and of these 8 had undergone operations on the labyrinth and are not included for the purposes of this discussion. Of the remaining 37, 26 were treated with nicotinic acid only, 7 were treated with nicotinic acid together with some other drug and 4 were treated entirely by drugs other than nicotinic acid.

The results of treatment are analysed in the following table:

| Total No. (under survey for more than five years) | Entirely free of vertigo for more than one year | Average time free of vertigo | Vertigo controlled | Useful hearing |
|---|---|---|---|---|
| 37 | 21 | 6½ years (Range: 18/12—11 yrs.) | 16 | 19 |

Two conclusions are emphasized. Firstly the long periods of complete remission that can occur after prolonged attacks of incapacitating vertigo from Ménière's disease. Secondly the high proportion of patients who still have useful hearing five years or more after the disease had been diagnosed. It is our clinical impression that treatment with nicotinic acid contributes to these favourable results.

REFERENCE

KODICEK, J. M., TAYLOR, L. R. S., and BATEMAN, G. H. (1950) *Proc. R. Soc. Med.*, **43**, 283.

# Section of Experimental Medicine and Therapeutics

President—J. V. Dacie, M.D., F.R.C.P.

[*February* 5, 1958]

## SYMPOSIUM ON HÆMOGLOBIN

**Professor C. Rimington** (London):

*The Biosynthesis of Hæmoglobin*

Approximately 8 grams of hæmoglobin are synthesized daily by the human adult to replace that broken down in the normal course of events. During recent years, the biochemical pathway by which the hæm moiety of hæmoglobin is synthesized from glycine, succinate and iron has been largely elucidated—but I shall consider the production of hæmoglobin as a whole and the temporal sequence of events in the maturing cell destined eventually to become an erythrocyte.

The molecule of hæmoglobin appears to be built up of several layers of coiled polypeptide chains with each of the four flat hæm residues probably lying against its surface. The hæms are fairly easily detached by relatively gentle chemical methods and recombination between hæm and undenatured globin is also possible so that one might well wonder whether, in the developing cell, globin is synthesized prior to hæm and the latter then attached to its surface.

In 1947 Thorell investigated this problem in the following manner. Cells of the erythropoietic series, seen in a bone-marrow preparation and at different stages of maturation, were subjected individually to microspectrographic examination using the appropriate wavelengths which would measure the contents of nucleic acid, total protein and hæm respectively. It was assumed that the figure for total protein could be accepted as equivalent to globin and by relating the data to the stage of maturation of the cell a time-sequence for each component was revealed, as shown in Fig. 1. Total protein synthesis appears quite definitely to precede that of hæm.

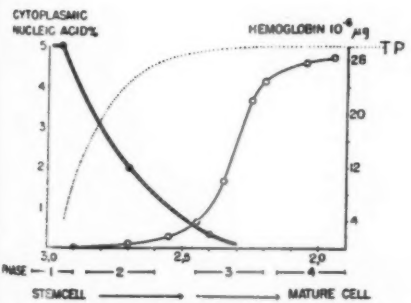



FIG. 1.—Decrease of nucleic acid (-●-●-) and synthesis of total protein (.....) and of hæm (-o-o-) in developing erythropoietic cells (reproduced from Thorell, 1947, by courtesy of the author and publisher).

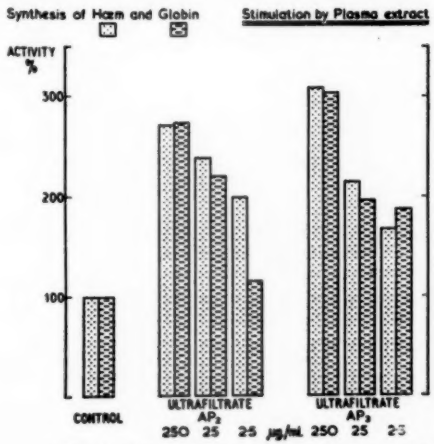



FIG. 2.—Parallel stimulation of hæm and of globin synthesis in dog's reticulocytes *in vitro* by an ultrafiltrable plasma factor.

Nine years later, Lagerlöf *et al.* (1956) arrived at the same conclusion from measurements made with the interference microscope which gave, in this case, values for the hæm and total dry mass per unit area of a series of cells from the bone-marrow. Since more than 90% of the solid content of a mature erythrocyte is hæmoglobin, the assumption was made that the measured increase in cell content could be regarded as biosynthesis of globin.

A quite different approach to the problem by Muir *et al.* (1952) led to a conclusion at variance with that of Thorell. They administered radioactive glycine to animals and took blood samples at intervals thereafter, measuring the radioactivity per mole of the hæm moiety and of the glycine isolated from the globin of each sample of hæmoglobin. From the first twenty-four hours onwards, the ratio was not significantly different from 8 as would be expected if globin and hæm were synthesized simultaneously from the same pool of glycine. Earlier than this, the ratio was definitely less than 8 which might suggest some prior synthesis of globin but without knowing exactly the sizes of the pools of globin and hæm respectively, it is difficult to draw a definite conclusion.

Hæmoglobin biosynthesis may also be studied *in vitro* using reticulocytes from animals made anæmic either by bleeding or by phenylhydrazine poisoning. Kruh and Borsook (1956) have used such systems incubated with 2-$^{14}$C-glycine and have found a parallelism between synthesis of globin and of hæm, as did Neuberger's group. The objection could, however, be raised that they measured the activity of their globin samples as a whole and did not isolate the glycine from the protein. Nizet (1953, 1955, 1957) has overcome this objection in a series of careful experiments in which dogs rendered anæmic by bleeding are used and the hæmoglobin crystallized prior to separation into globin and pigment moieties. Free porphyrins are also carefully removed before the hæm activity is measured and the globin is hydrolysed by boiling with acid and its constituent glycine then isolated as the pure dinitrophenyl derivative. Radioactive carbon is counted in each case as barium carbonate.

Nizet's results again demonstrate simultaneity in the biosynthesis of globin and of hæm by the normal reticulocyte.

Using this system, he has also studied the effect of stimulating or inhibiting the production of one or other component of hæmoglobin by addition of suitable substances. Thus, ferrous sulphate is known to enhance hæm production in isolated systems. When added to reticulocyte preparations not only hæm synthesis but also that of globin was stimulated and each to an approximately equal degree. In an analogous manner, addition of lead acetate inhibited both syntheses to a comparable degree.

An even more striking parallelism between globin and hæm biosynthesis was brought about by addition of a stimulating factor derived from plasma. This material is under study by Nizet and myself. It is present in an ultrafiltrate prepared from a plasma albumin fraction and appears to differ from any hitherto known hæmopoietic stimulant. When added to a chick hæmolysate system, it markedly increases hæm formation and when applied to intact reticulocytes, both hæm and globin formation are found to be stimulated in parallel manner (Fig. 2).

It would appear from these and other experiments that, in the intact dog reticulocyte at any rate, there must be some mechanism by which the synthesis of globin is regulated and controlled by that of hæm. We know that under certain conditions this delicate interdependence may be broken down, as for example by irradiation or by hæmolysis of the cell which completely stops protein synthesis whilst permitting that of hæm to continue. Even small variations in tonicity, insufficient to cause rupture of the chicken red cell membrane, will impair globin synthesis, according to unpublished experiments performed by Goldberg in my laboratory. The mechanism of adjustment is therefore a very delicate one but it is difficult to see how one can escape the conclusion from the experiments to which I have referred that in the normal cell the synthesis of globin is governed by that of hæm. The discrepancy between the experiments of Lagerhöf *et al.* (1956), in which total protein synthesis was measured in the maturing cell, and those by which the globin of hæmoglobin was specifically measured suggests that we may have to look for a "pre-globin" of some kind and in this connexion it is interesting to recall that Schweiger *et al.* (1956) present evidence supporting the synthesis of hæmoglobin in surviving rabbit reticulocytes at the expense of the stroma protein of these cells. This problem with its two aspects, the relation of globin to other proteins of the developing cell and the mechanism of the interdependence between hæm synthesis and globin synthesis is of a most interesting character and invites further work leading to ultimate solution; it has practical as well as theoretical importance.

## REFERENCES


KRUH, J., and BORSOOK, H. (1956) *J. biol. Chem.*, **220,** 905.

LAGERLÖF, B., THORELL, B., and ÅKERMAN, L. (1956) *Exp. Cell Res.*, **10,** 752.

MUIR, H. M., NEUBERGER, A., and PERONNE, J. C. (1952) *Biochem. J.*, **52,** 87.

NIZET, A. (1953) *Rev. méd. Liège*, **8,** 506.

—— (1955) *Rev. méd. Liège*, **10,** 392.

—— (1957) *Bull. Soc. Chim. biol., Paris*, **39,** 265.

SCHWEIGER, H. G., RAPOPORT, S., and SCHÖLZEL, E. (1956) *Nature, Lond.*, **178,** 141.

THORELL, B. (1947) Studies on the Formation of Cellular Substances During Blood Cell Production. London; fig. 48, p. 90.

**Dr. A. C. Allison** (London):

*The Genetical and Clinical Significance of the Haptoglobins*

The term "haptoglobin" has been applied by Jayle to a group of plasma proteins having the distinctive property of combining with hæmoglobin (Jayle, 1939; Jayle and Boussier, 1955). The common form of haptoglobin in human plasma has been isolated and shown to be a glycoprotein of molecular weight about 170,000 (Jayle *et al.*, 1956). When submitted to electrophoresis in the Tiselius apparatus or on filter paper, haptoglobin migrates with the $\alpha_2$ globulins; the complex with hæmoglobin migrates with the $\beta_1$ fraction and free hæmoglobin migrates between the $\beta$ and $\gamma$ fractions (Jayle *et al.*, 1952; Laurell and Nyman, 1957*a*). The complex of haptoglobin and hæmoglobin has peroxidative activity, and this reaction affords one method of estimating the concentration of haptoglobin in plasma (Jayle and Boussier, 1955).

Smithies (1955), using electrophoresis with starch gels as supporting medium, showed that the sera of normal human subjects fall into three groups. It has since become clear that the determinant proteins are haptoglobins, and Smithies and Walker (1956) have suggested that the groups should be termed haptoglobin types 1-1, 1-2 and 2-2. The features distinguishing these groups have been described in detail by Allison and ap Rees (1957) and are shown in Fig. 1.

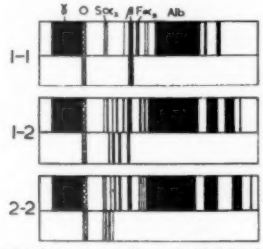



FIG. 1.—Patterns obtained by submitting sera from individuals of the three common haptoglobin types to electrophoresis in starch gels (borate buffer, pH 8·4, ionic strength 0·1). The upper pattern in each pair shows all serum proteins, from left to right: $\gamma$ globulin, origin, slow $\alpha_2$ globulin, post-$\beta$ and $\beta$ globulin, fast $\alpha_2$ globulin, post-albumin, albumin and pre-albumin. The lower patterns show the haptohæmoglobin complexes, as stained with benzidine.

*Inheritance of Haptoglobin Types*

Extensive family data collected by Smithies and Walker (1956), Galatius-Jensen (1958) and the author have shown that the haptoglobins are inherited in regular manner. The simplest genetic hypothesis consistent with most of the available data, proposed by Smithies and Walker, is that a single pair of genes, $Hp^1$ and $Hp^2$, account for the three types. Subjects of type 1-1 are supposed to be homozygous for $Hp^1$, and of type 2-2 to be homozygous for $Hp^2$, whereas subjects of type 1-2 are the heterozygotes, $Hp^1/Hp^2$. This hypothesis implies that a single gene ($Hp^2$) controls the formation of three distinct proteins, which is without precedent in genetics. The author considers it more likely that the inheritance of the haptoglobins is controlled by four closely linked genes behaving as a "super-gene" in much the same way as the four genes of the Rh blood-group complex. Nevertheless, the distinction between these two alternatives is a difficult problem in genetics having little practical application, so that the interpretation of Smithies and Walker can be used as a working hypothesis.

What this interpretation cannot explain, however, is the finding that about 2% of healthy British adults, and about 30% of healthy Nigerian adults, have no demonstrable haptoglobins at all (Allison *et al.*, 1958). The data of Galatius-Jensen (1958) and the author exclude the possibility that such persons are homozygous for another gene at the same locus (behaving like O in the ABO blood-group system). An alternative explanation is the existence of a recessive suppressor gene at another locus which in double dose suppresses the appearance of haptoglobins in plasma. Analogies would be the *x* and *y* genes which when homozygous suppress the appearance of the B and O and A antigens, respectively, in persons possessing the corresponding blood-group genes (Levine *et al.*, 1955; Weiner *et al.*, 1957).

*Concentration of Haptoglobins in Normal Subjects*

The concentration of haptoglobin in plasma or serum is usually measured in terms of hæmoglobin-combining power. Jayle's (1951) results, using the development of peroxidative activity as an index of haptoglobin concentration, correspond to a hæmoglobin-combining

power of 100 ± 40 mg. per 100 ml. serum. Laurell and Nyman (1957*a*) using a filter paper electrophoretic method, give a mean value of 90 mg. per 100 ml., with a normal range of 40 to 150 mg. Using the somewhat more sensitive method of starch gel electrophoresis, Allison and ap Rees (1957 and unpublished) have found a mean value of 120 mg. with a standard deviation of 26 mg. in types 1-1 and 1-2, and 100 ± 20 mg. in type 2-2.

In umbilical cord blood haptoglobins are usually lacking altogether (Tuttle, 1955; Allison and ap Rees, 1957; Galatius-Jensen, 1958). As a rule the sera develop demonstrable haptoglobins by the end of the second week of postnatal life. In all cases so far examined the adult haptoglobin pattern is fully developed by the fourth month, a point of medico-legal interest.

*Haptoglobins in Hæmolytic Anæmias and Hæmoglobinurias*

The most striking property of haptoglobins is their ability to combine with hæmoglobin. The fate of the haptoglobins when hæmoglobin is released into the plasma as a result of intravascular hæmolysis is therefore of interest.

The effect of a single release of a relatively large amount of hæmoglobin can be simulated by an intravenous injection of the protein. This has been carried out in human subjects by Ottenberg and Fox (1938), Gilligan *et al.* (1941) and Laurell and Nyman (1957*a*, *b*). The results of these authors are in good agreement. When the concentration of hæmoglobin in the plasma does not rise above 80–140 mg. (the level varying slightly from subject to subject) no hæmoglobinuria occurs. The correspondence between this level and the hæmoglobin-combining power of the haptoglobins led Laurell and Nyman (1957*a*, *b*) and Allison and ap Rees (1957) independently to formulate a new explanation for the "renal threshold" for hæmoglobin, in place of the previously held concept of a limit to tubular reabsorption of hæmoglobin. According to the new interpretation, hæmoglobin bound to haptoglobin (in the form of a complex of molecular weight about 300,000) would not appear in the glomerular filtrate at all, whereas free oxyhæmoglobin seems to pass freely into the glomerular filtrate. Hence hæmoglobinuria would only be expected when the level of oxyhæmoglobin in the plasma exceeds the combining power of the haptoglobins. This situation is shown nicely in Laurell and Nyman's (1957*b*) experiment, illustrated in Fig. 2,

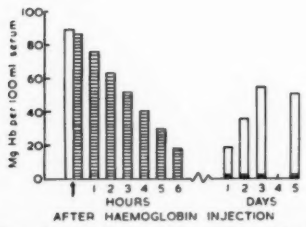



FIG. 2.—Concentration of free (shaded) and bound hæmoglobin in plasma and concentration of hæmoglobin in the urine after two injections of hæmoglobin (Laurell and Nyman, 1957*b*, reproduced by courtesy of the authors and of the Elsevier Publishing Company, Amsterdam).

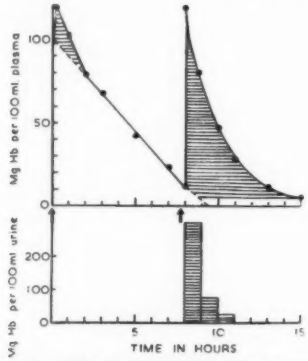



FIG. 3.—The concentration of free haptoglobin and haptohæmoglobin (shaded) after a single injection of hæmoglobin (Laurell and Nyman, 1957*a*, reproduced by courtesy of the authors and of Grune and Stratton, Inc., New York).

where a single injection of hæmoglobin gave rise to no hæmoglobinuria but saturated the haptoglobins so that a subsequent injection produced well-marked hæmoglobinuria. Such sudden intravascular releases of hæmoglobin would occur clinically in incompatible blood transfusion, accidental intravenous infusion of distilled water, blackwater fever and some other conditions. Acute lysis of about 1% of the circulating cells would be sufficient to produce hæmoglobinuria.

Thus hæmoglobin in the plasma in concentrations below about 100 mg. per ml. is not removed by the kidneys. Nevertheless, after a hæmoglobin injection the concentration in the plasma falls steadily for about eight hours, giving a linear plot against time (Laurell and Nyman, 1957*a*, Fig. 3). In other words, the removal of the haptohæmoglobin complex

TABLE I.—HAPTOGLOBINS IN HÆMOLYTIC ANÆMIAS AND RELATED TRAITS

| Case No. | Diagnosis | Plasma Hb (mg./100 ml.) | Haptoglobin conc. (mg. Hb/100 ml.) | Haptoglobin type | Hæmoglobinuria | Hæmosiderinuria |
|---|---|---|---|---|---|---|
| 0 | Normal | 4 | 85 to 135 | — | — | — |
| 1 | Acquired hæmolytic anæmia | 13 | 15 | 1:2 | — | — |
| 2 | Acquired hæmolytic anæmia | 9 | 45 | 1:2 | — | — |
| 3 | Acquired hæmolytic anæmia | 27 | 0 | ? | — | + |
| 4 | Hereditary spherocytosis (presplenectomy) | 8 | 0 | ? | — | + |
| 5 | Sickle-cell disease | 15 | 0 | ? | — | + |
| 6 | Sickle-cell disease | 21 | 0 | ? | — | + |
| 7 | Sickle-cell trait | 3 | 120 | 1:2 | — | — |
| 8 | Sickle-cell trait | 5 | 85 | 2:2 | — | — |
| 9 | Sickle-cell trait | 4 | 130 | 1:1 | — | — |
| 10 | Hæmoglobin C trait | 5 | 120 | 1:1 | — | — |
| 11 | Thalassæmia major | 23 | 0 | ? | — | + |
| 12 | Thalassæmia major | 20 | 0 | ? | — | + |
| 13 | Thalassæmia minor | 14 | 30 | 2:2 | — | — |
| 14 | Thalassæmia minor | 7 | 85 | 1:2 | — | — |
| 15 | Pernicious anæmia (untreated) | 18 | 0 | ?(2:1) | — | + |
| 16 | Pernicious anæmia (untreated) | 23 | 0 | ?(2:2) | — | + |
| 17 | Pernicious anæmia (treated) | 5 | 100 | 1:1 | — | — |
| 18 | Pernicious anæmia (treated) | 3 | 120 | 1:2 | — | — |
| 19 | Pernicious anæmia (treated) | 4 | 100 | 1:2 | — | — |
| 20 | Pernicious anæmia (treated) | 3 | 125 | 1:2 | — | — |
| 21 | Pernicious anæmia (treated) | 5 | 95 | 1:2 | — | — |
| 22 | Pernicious anæmia (treated) | 3 | 85 | 2:2 | — | — |
| 23 | Pernicious anæmia (treated) | 2 | 90 | 2:2 | — | — |
| 24 | Hæmolytic disease of the newborn | 6 | 0 | ? | — | — |
| 25 | Hæmolytic disease of the newborn | 5 | 0 | ? | — | — |
| 26 | Paroxysmal nocturnal hæmoglobinuria | 45 | 0 | ? | + | + |
| 27 | Paroxysmal nocturnal hæmoglobinuria | 57 | 0 | ? | + | + |
| 28 | Paroxysmal nocturnal hæmoglobinuria | 38 | 0 | ? | + | + |
| 29 | Paroxysmal nocturnal hæmoglobinuria | 65 | 0 | ? | + | + |
| 30 | Paroxysmal nocturnal hæmoglobinuria | 10 | 135 | 1:2 | — | — |
| 31 | Paroxysmal nocturnal hæmoglobinuria | 25 | 60 | 1:2 | — | ? |
| 32 | Cold hæmoglobinuria | 13 | 0 | ? | + | + |
| 33 | Cold hæmoglobinuria (after recovery) | 5 | 0 | ? | — | — |
| 34 | Cold hæmoglobinuria (after recovery) | 6 | 100 | 1:2 | — | — |
| 35 | Cold hæmolysis | 9 | 80 | 1:2 | — | — |
| 36 | Cold hæmolysis | 7 | 110 | 2:2 | — | — |
| 37 | March hæmoglobinura (after recovery) | 25 | 50 | 1:2 | — | — |
| 38 | Hepatic cirrhosis | 7 | 0 | ? | — | + |
| 39 | Hepatic cirrhosis | 5 | 30 | 1:2 | — | — |

UNIVERSITY OF MICHIGAN LIBRARIES

follows zero order kinetics, which implies that the organs concerned—presumably the liver and/or reticulo-endothelial system—can metabolize the complex at only a limited rate: about 400 mg. per hour in the whole body or 13 mg. per 100 ml. plasma per hour.

Whether haptoglobin is released from the complex is unknown, but the relatively slow reappearance of haptoglobin in the plasma after a single hæmoglobin injection (Fig. 3) corresponds to the known rate of replacement of other globulins, which seems to imply *de novo* synthesis. Studies of the rate of turnover of labelled haptoglobins would be of interest.

It is therefore reasonable to suppose that with continuous intravascular hæmolysis the rate of hæmoglobin release might exceed the rate of haptoglobin replacement. The concentration of haptoglobin in the plasma would then be below normal or even fall to zero. This expectation is borne out in practice (Table I). There is also fairly good agreement between the absence of haptoglobins and the presence of hæmoglobinuria or hæmosiderinuria, the latter presumably resulting from microscopical hæmoglobinuria followed by tubular reabsorption and breakdown of hæmoglobin. An exception is hæmolytic disease of the newborn, in which the lack of hæmoglobinæmia and hæmoglobinuria may be due to hæmolysis resulting in the main from removal of intact cells coated with antibody from the circulation.

The absence of haptoglobin in these conditions seems to be secondary to continued hæmoglobinæmia. It does not always occur, however. Through the courtesy of Professor J. V. Dacie and Dr. J. G. Selwyn, the author has been able to examine the sera of two patients with the typical paroxysmal nocturnal hæmoglobinuria defect in their erythrocytes and moderate hæmoglobinæmia but no hæmoglobinuria (Cases 30 and 31 in Table I). Both had haptoglobins, the concentration in one being well below the limit of normality.

One other point deserves mention. In analyses of sera from a series of patients with hæmolytic syndromes, Allison and ap Rees (1957) found methæmalbumin only when the concentration of oxyhæmoglobin exceeded the combining-power of haptoglobins. The complexing of oxyhæmoglobin with haptoglobin seems to stabilize the pigment and prevent the splitting off and oxidation of hæm and its attachment to albumin.

*Haptoglobins in Other Diseases*

The occurrence of several haptoglobin types side by side in several human populations represents a true polymorphism, like those of the blood groups in all human populations and the hæmoglobin types in parts of Africa and Asia. For theoretical reasons (Ford, 1945; Allison, 1955) it is likely that such polymorphisms are maintained by a balance of selective forces acting upon the different genotypes. Thus, there is substantial evidence that resistance of the sickle-cell heterozygote against falciparum malaria helps to counterbalance the loss of sickle-cell genes through anæmia (Allison, 1957). And in recent years it has become clear that the possession of certain blood groups affects susceptibility to various diesases (*see* Fraser-Roberts, 1957).

In analysing the haptoglobins in subjects with different diseases, therefore, two points are worth bearing in mind. The first is the susceptibility of the different genotypes to disease. The relatively small number of individuals so far tested would, however, show such a relationship only if it were very striking. The second point is the existence of phenotypic changes in the concentration and nature of haptoglobins which might provide some clues to their physiological and genetical significance.

It has already been stated that the haptoglobins determine the renal threshold for hæmoglobin and are absent in chronic hæmoglobinurias. This indicates one physiological function for haptoglobin. The binding of plasma hæmoglobin in the plasma prevents the loss of this substance from the body through the kidneys and must play a part in iron retention, upon which the critical iron balance in the body depends.

Nevertheless, it seems unlikely that natural selection would have conserved four distinct haptoglobins in the plasma solely to bind hæmoglobin released by intravascular hæmolysis. The search for other possible functions of haptoglobins has not yet yielded much information. The author has found that haptoglobins are not concerned in the transport of iron, copper or iodine in the plasma. Latner and Zaki (1957) reported that the amount of radioactive vitamin $B_{12}$ bound by serum proteins migrating in the $\alpha\beta$ region in starch gel electrophoresis is very much higher per unit weight of protein than in any other region. This finding suggests that the haptoglobins (3 of which migrate in the $\alpha\beta$ region) might be concerned with transport of vitamin $B_{12}$ in the plasma; their glycoprotein nature would be compatible with such a function. This argument led the author to consider whether it could be subjects congenitally lacking haptoglobins who develop pernicious anæmia in late middle age. Two untreated cases of pernicious anæmia did, in fact, fail to show haptoglobins; but the interest generated by this finding subsided when typical haptoglobins

appeared within one week of instituting treatment, and attained normal levels after about three weeks of treatment. A number of other treated cases also showed typical haptoglobins (Table I), so that the absence of these proteins in the untreated cases is presumably a phenotypic change secondary to hæmolysis. Similar findings in 8 cases of pernicious anæmia have been reported by Nyman (1957).

Jayle and his colleagues have found that serum haptoglobin levels are considerably raised in a variety of diseases in which there is inflammation or destruction of tissue, including acute pyogenic infections, rheumatic fever and some cancers (*see* Jayle and Boussier, 1955). Allison and Blumberg (1958) reported that the haptoglobin concentration is nearly always very high in acute rheumatoid arthritis. The significance of these findings is at present obscure. The haptoglobins probably represent part of the serum glycoprotein fraction that has been found to be elevated in rheumatoid arthritis and some other conditions. In this connexion it is noteworthy that the marked increase in concentration of $\alpha_2$ globulins in the sera of women receiving large doses of androgens appears to be due very largely, if not entirely, to an increase in haptoglobin (Studnitz and Nyman, 1957). The interesting suggestion of Jayle and Boussier (1955) that haptoglobins are connective tissue proteins secondarily released in the blood—in increased quantities when there is connective tissue breakdown—cannot yet be either proved or disproved. Studies with labelled haptoglobins would also be of value in this problem.

The absence of haptoglobins in about one-third of Nigerian adults is remarkable from the point of view of population genetics. These individuals must have recurrent hæmoglobinæmia from malaria in childhood, which in the absence of haptoglobins would be expected to lead to significant iron depletion. Hence one would deduce that the absence of haptoglobins would be disadvantageous, in spite of which the trait remains remarkably common. The simplest explanation is that (as in the case of the sickle-cell character) persons heterozygous for the gene concerned are favoured by selection. At present we do not know even where to direct our search for such an advantage.

## REFERENCES


ALLISON, A. C. (1955) *Cold Spr. Harb. Symp. quant. Biol.*, **20,** 239.
—— (1957) *Exp. Parasit.*, **6,** 418.
——, and AP REES, W. (1957) *Brit. med. J.*, ii, 1137.
——, and BLUMBERG, B. S. (1958) *Arthr. & Rheum.*, **1,** 239.
——, ——, and AP REES, W. (1958) *Nature, Lond.*, **181,** 824.
FORD, E. B. (1945) *Biol. Rev.*, **20,** 73.
GALATIUS-JENSEN, F. (1958) *Acta genet.*, **7,** 549.
GILLIGAN, D. R., ALTSCHULE, M. D., and KATERSKY, E. M. (1941) *J. clin. Invest.*, **20,** 177.
JAYLE, M-F. (1939) *Bull. Soc. Chim. biol., Paris*, **21,** 14.
—— (1951) *Bull. Soc. Chim. biol., Paris*, **33,** 876.
——, and BOUSSIER, G. (1955) *Expos. ann. Biochim. méd.*, **17,** 157.
——, ——, and BADIN, J. (1952) *Bull. Soc. Chim. biol., Paris*, **34,** 1063.
——, ——, and TONNELAT, J. (1956) *Bull. Soc. Chim. biol., Paris*, **38,** 343.
LATNER, A. L., and ZAKI, A. H. (1957) *Biochem. J.*, **66,** 54P.
LAURELL, C. B., and NYMAN, M. (1957*a*) *Blood*, **12,** 493.
——, —— (1957*b*) *Clin. Chim. Acta*, **3,** 220.
LEVINE, P., ROBINSON, E., CELANO, M., BRIGGS, O., and FALKINBURG, L. (1955) *Blood*, **10,** 1100.
NYMAN, M. (1957) *Scand. J. clin. Lab. Invest.*, **9,** 168.
OTTENBERG, R., and FOX, C. L., Jr. (1938) *Amer. J. Physiol.*, **123,** 516.
ROBERTS, J. A. F. (1957) *Acta genet.*, **6,** 549.
SMITHIES, O. (1955) *Biochem. J.*, **61,** 629.
——, and WALKER, N. F. (1955) *Nature, Lond.*, **176,** 1265.
——, —— (1956) *Nature, Lond.*, **178,** 694.
STUDNITZ, W. v., and NYMAN, M. (1957) *J. clin. Endocrin.*, **17,** 910.
TUTTLE, A. H. (1955) *Science*, **121,** 701.
WEINER, W., LEWIS, H. B. M., MOORES, S., SANGER, R., and RACE, R. R. (1957) *Vox Sanguinis*, **2,** 25.


**Dr. V. M. Ingram** (Cambridge):

*Abnormal Human Hæmoglobins*

Neel demonstrated in 1949 that sickle-cell anæmia is a disease inherited in a strictly Mendelian manner, and Pauling and his colleagues showed in the same year that the blood of sickle-cell patients contains a hæmoglobin which differs electrophoretically from normal hæmoglobin. Since then, several other abnormal hæmoglobins have been discovered. They have been studied intensively by many workers for the sake of both their medical and their genetic interest, because they provide one of the clearest cases where mutations in a Mendelian gene are reflected in changes in the chemical structure of a protein. The medical aspect is important because several of the abnormal hæmoglobins give rise to severe

hæmolytic anæmias, which thus provide one of the rare instances when a disease is directly attributable to an inherited change in a protein molecule. Like other proteins, hæmoglobin is thought to be the first protein product of the gene. The sequence and spacing of the mutations on the gene responsible for its synthesis should therefore be reflected in the sequence and spacing of the changes in amino-acid composition which these mutations produce in the hæmoglobin.

Chemical studies on hæmoglobins A (normal) and S (sickle-cell) by previous authors may be summarized by saying, first, that whatever difference exists between them must be small, and secondly, that the known charge difference of two to three units per molecule is probably due to hæmoglobin S having fewer carboxyl groups. When it is remembered that human hæmoglobin is made up of two identical halves, this difference is probably one of a single carboxyl group in the half-molecule. It was not known whether the two hæmoglobins differed in amino-acid sequence or, on the other hand, in the folding of the polypeptide chains leading to masking of some groups. We can now say for certain that there is a difference in amino-acid composition and that this does involve a carboxyl group, and explain the known electrophoretic behaviour. In fact, the polypeptide chains of the two hæmoglobins differ in only one amino-acid residue; one of the glutamic acid residues of hæmoglobin A had changed to valine in hæmoglobin S. No other changes could be detected.

Another mutation of the same hæmoglobin gene produces another abnormal protein, hæmoglobin C. This causes a severe anæmia only when it occurs together with hæmoglobin S. The solubility of hæmoglobin C is almost normal and so is its amino-acid composition; however, it is easily distinguished electrophoretically, since it has even fewer net negative charges per molecule than hæmoglobin S which itself has two fewer than the hæmoglobin A molecule.

The same amino acid, glutamic acid, of normal hæmoglobin has changed also in the hæmoglobin C mutation; its place is taken by lysine. In each half-molecule a negatively charged side chain has been replaced by a positive group altering the net charge of the protein by four units, twice as many as for hæmoglobin S.

Genetic evidence shows that the hæmoglobin S and the hæmoglobin C mutations are allelic, i.e. that they occur in the same locus. In the two mutations the same very small portion of the hæmoglobin gene seems to be affected and in turn the identical amino acid in the polypeptide chain is replaced by either valine or lysine in hæmoglobin S and C respectively.

REFERENCES

NEEL, J. V. (1949) *Science*, **110**, 64.
PAULING, L., ITANO, H. A., SINGER, S. J., and WELLS, I. C. (1949) *Science*, **110**, 543.

**Dr. J. H. Walters** (London):

*Vascular Occlusion in Sickle-cell Disease*

Sickle-cell anæmia resembles other types of chronic hæmolytic anæmia in that its course is punctuated by recurrent "crises". It is unlike any other type of chronic hæmolytic anæmia in that with the hæmolytic process there is associated a marked tendency towards spontaneous vascular occlusion. The relative contribution of each of these two processes to the production of crises is a matter of controversy. Prior to 1956, all reports stress the occurrence of crises of hæmolysis, and although the development of thromboses is noted, for instance by Margolies (1951) and by Mabayoje (1956) little importance is attributed to this factor in the pathogenesis of the disease. Diggs, however, in 1956 published the results of his careful and prolonged observation of 166 cases of sickle-cell anæmia in Memphis, Tennessee, during which he noted the occurrence of 747 episodes or "crises", in none of which was there evidence of an exacerbation of hæmolysis: he was convinced that vascular occlusion was the sole mechanism involved. Harris *et al.* (1956) demonstrated the occurrence of increases in blood viscosity, ranging from 43% to 115%, when the oxygen tension to which sickle-cell anæmia blood is exposed is lowered to 40 mm.Hg, which is within the physiological range of the partial pressure of oxygen in the capillaries of many organs. This increase in viscosity is due to the development of the sickle deformity in the anoxic erythrocytes causing increased frictional resistance to flow. Vascular occlusion is attributed by Harris *et al.* to capillary blockage by plugs of interlocked sickle cells, on which a thrombus ultimately forms.

Recently, in a report on the natural history of sickle-cell anæmia as seen in Central Africa, Trowell *et al.* (1957) have noted the frequent occurrence of osteopathy of the bones of the hands and feet attributable in my opinion to infarction—but have also observed hæmolytic crises, though these were infrequent. My own experience, obtained in Nigeria, in a series of 16 patients suffering from this disease, suggests that the natural history of the disease is dominated by episodes of infarction, while hæmolytic crises are rare.

Two events observed in this series suggested that factors likely to influence the coagulability of the plasma might precipitate multiple infarction. The first patient, who had gross hepatomegaly, was given daily 10 mg. of vitamin K for three days prior to liver biopsy, which was carried out uneventfully under local anæsthesia. On the second day after biopsy, increasing hepatomegaly was noticed with a rising temperature. She died twenty-four hours later of acute peripheral circulatory collapse and at autopsy multiple fresh infarctions were found in the kidneys, suprarenals and the liver. Such sinusoidal thrombi were not found in the biopsy specimen. A second patient, under treatment in an orthopædic ward for a traumatic fracture of the left femur, was given a transfusion of two pints of compatible, non-sickling blood. After eighteen hours she had a convulsion, increasing hepatomegaly with jaundice of obstructive type was evident, acute synovial effusions appeared in the left knee and ankle joints, albumin, red cells, casts and leucocytes were found in the urine and abdominal distension due to ileus developed. She appeared to have suffered widespread infarctions in the liver, kidneys, mesenteric system and the synovia: she recovered slowly over the next seven days. Turning to Diggs' (1956) monograph on the clinical course of the disease which is illustrated by a series of charts, I was interested to observe that several of these appear to show similar sequelæ to blood transfusion and, in one patient, to injection of T.A.B. vaccine: Bauer (1940) also has reported a fatal "crisis" following compatible blood transfusion.

It would appear, therefore, that capillary occlusions are particularly liable to follow procedures which might increase the coagulability of the plasma, even though one of them, blood transfusion, should diminish the concentration of erythrocytes capable of forming interlocked aggregations under conditions of anoxia, and should diminish the anoxia itself.

Since the liver in sickle-cell anæmia appears to undergo progressive enlargement and fibrosis with increasing age, it seemed worth while to investigate this organ as representative of the parenchymatous organs of the body as a whole, especially as its rich and sluggish capillary bed, and its high oxygen uptake should render it peculiarly susceptible to vascular blockage in this disease. Liver biopsy was therefore carried out on each patient. The most striking findings, which were present in every specimen, comprised wide dilatation of the sinusoids together with the presence within their lumen of a delicate, foam-like, reticulum. This structure stained homogeneously pink with hæmatoxylin-eosin, mauve with Gram Weigert stain, and could be impregnated with silver. It appeared to be composed of fibrin. It was demonstrable in both alcohol-fixed and formol-fixed material, obtained either by biopsy or at post-mortem. In formol-fixed specimens, in which the red cells are preserved in the sickled form, they can be seen lying in the interstices of this reticulum. I have seen no similar structure in the sinusoids of very many liver biopsy specimens from African children which were obtained, fixed and stained in an identical manner.

The intra-luminal fibrin reticulum appears to be in continuity with the longitudinal fibres of the sinusoidal wall—the linear thickenings of the peri-sinusoidal membrane (Elias, 1950) —and seems in time to be incorporated into them. In older subjects, this process may result in a gross lamellar thickening of the peri-sinusoidal membrane, leading to a diffuse fibrosis causing total disruption of the normal stromal architecture. This process explains the characteristic appearances in the advanced case in which the wall of the liver cell is separated by a wide zone of loose fibrous tissue from the endothelial wall of the patent, though narrowed, sinus.

The same structure has apparently been observed by other workers. Song (1957) reports a "fibrin-like network" and "hyaline thrombi" in the sections of autopsy liver specimens, Diggs and Bruegge (1954) refer to increased numbers of platelets "which tend to congregate and to blockade capillaries", while Murphy and Shapiro (1945), in a biopsy specimen taken during a "crisis" from a tender subcutaneous node, reported that "the capillaries, arterioles and venules were crowded with and slightly distended by sickled erythrocytes and a delicate fibrin meshwork". Vanderpitte and Louis (1953) in wet preparations of marrow aspirate in sickle-cell anæmia have described a structure "somewhat like a dense mycelium", and regarded it as diagnostic of the disease. The origin of this reticular fibrinoid structure is uncertain; it has been attributed to platelet aggregation (but is not observed in other forms of chronic hæmolytic anæmia in which a comparable increase in circulating platelets is to be found), and to the distorted residual envelopes of lysed red blood cells (which would imply a very extensive intravascular hæmolysis of which there is no other evidence). It seems more probable that it represents the intravascular precipitation of fibrin from the plasma during life.

Little investigation of the plasma has been carried out in this disease, and my own studies were interrupted at a very early stage. Fenichel *et al.* (1950) found a lowered serum albumin in 13 out of 15 cases (av. 3·43 grams/100 ml.), a raised gamma globulin in 12 out of 15 (av. 1·83 grams/100 ml., normal 1·06 grams) and an increased fibrinogen concentration in 8 out of 10 (av. 0·67 gram/100 ml., normal 0·34), while Murphy and Shapiro (1945) noted

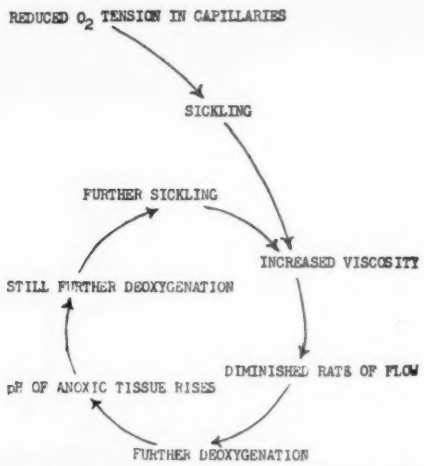



FIG. 1.—Diagram illustrating sequence of events leading to capillary occlusion in sickle-cell anæmia, according to Harris *et al.* (1956).

increased prothrombin activity, which was further augmented during "crisis", and also hyper-fibrinogenæmia in a single patient. In my series, two sets of coagulation-time estimations by Wintrobe's (1951) method showed that this was significantly shortened in 6 out of 7 patients while prothrombin concentration in the plasma was increased, compared with that of a pooled specimen from healthy local Africans, in 10 out of 12 patients.

The explanation of the remarkable tendency towards capillary occlusion in sickle-cell anæmia suggested by Harris *et al.* (1956) and recorded in Fig. 1 may well be incomplete, for the findings which I have described suggest the presence of increased plasma coagulability. This may be a secondary result of ischæmic tissue damage, to which the increase in blood coagulability following coronary thrombosis bears analogy. On the other hand, the genetically-determined variation in the globulin fraction of hæmoglobin may be repeated in certain of the plasma protein components, increasing their coagulability, or a linked genetic factor may achieve this effect. Whatever the mechanism, I suggest that the spontaneous precipitation of a fibrin reticulum within the lumen of certain organs in life plays an important part in the pathogenesis of the disease. I would like to make a plea for further investigation of the plasma protein constituents in this disease.

## REFERENCES

BAUER, J. (1940) *Arch. Surg., Chicago*, **41**, 1344.
DIGGS, L. W. (1956) *Amer. J. clin. Path.*, **26**, 1109.
——, and BRUEGGE, C. F. V. (1954) *J. nat. med. Ass., Tuskegee, Ala.*, **46**, 46.
ELIAS, H. (1950) *Amer. J. Anat.*, **85**, 379.
FENICHEL, R. L., WATSON, J., and EIRICH, F. (1950) *J. clin. Invest.*, **29**, 1620.
HARRIS, J. W., BREWSTER, H. H., HAM, T. H., and CASTLE, W. B. (1956) *Arch. intern. Med.*, **97**, 145.
MABAYOJE, J. O. (1956) *Brit. med. J.*, i, 194.
MARGOLIES, M. P. (1951) *Medicine, Baltimore*, **30**, 357.
MURPHY, R. C., and SHAPIRO, S. (1945) *Ann. intern. Med.*, **23**, 376.
SONG, Y. S. (1957) *Amer. J. Path.*, **33**, 331.
TROWELL, H. C., RAPER, A. B., and WELBOURN, H. F. (1957) *Quart. J. Med.*, n.s. **26**, 401.
VANDERPITTE, J. M., and LOUIS, L. A. (1953) *Lancet*, ii, 806.
WINTROBE, M. M. (1951) Clinical Hæmatology. 3rd edit. London.

# Section of Medicine

President—W. A. BOURNE, M.A., M.D., F.R.C.P.

[*March* 25, 1958]

## DISCUSSION ON THE LUNGS AS AN INDEX OF SYSTEMIC DISEASE [*Abridged*]

**Dr. J. G. Scadding** (London):

I shall take the title "The Lungs as an Index of Systemic Disease" to refer to a practical situation—that which confronts the physician when he is faced with clinical or radiological evidence of abnormality in the lungs which may be the first evidence of a disease-process which involves or will involve other organs. I shall not discuss lung changes appearing in the course of already recognized or recognizable disease affecting other organs; and in order to limit the large field of discussion, I shall not refer to those acute systemic infections, ranging from chicken-pox to plague, which may have pulmonary manifestations. Even within these limitations I shall discuss only a few important points.

First, I should like to make briefly one or two rather commonplace observations.

*Acute forms of pulmonary tuberculosis* in middle-aged people, especially in the absence of any other obvious debilitating factors, may owe their acute nature to hitherto undiagnosed diabetes. *Collapse-consolidation of the lower lobe of the right lung* with or without pleural effusion may be the first evidence of subdiaphragmatic inflammatory changes, such as subphrenic abscess or amœbic abscess of the liver. *Pleural effusions* in general present many fascinating diagnostic problems. They are one of the more frequent intrathoracic manifestations of the collagen diseases. A malignant pleural effusion may owe its origin to an undiagnosed primary tumour in almost any part of the body. I imagine that many of us must at one time or another have looked hopefully for the benign fibroma of the ovary whose association with persistent pleural effusion constitutes Meigs' syndrome (Meigs and Cass, 1937; Meigs, 1954). I have never been fortunate enough to encounter one in my personal experience. *Frequently recurring broncho-pulmonary infections* with or without episodes of pulmonary consolidation may be due to abnormalities within the respiratory system, but sometimes they are due to disease involving other systems. For instance, the patient with achalasia of the cardia may have recurrent episodes of aspiration pneumonia due to spill-over from the dilated œsophagus, and sometimes it is these, rather than dysphagia, which first lead him to seek medical advice. Recurrent and chronic broncho-pulmonary infections are among the most important manifestations of mucosis, or fibrocystic disease of the pancreas, as it used to be called (Bodian, 1952). Especially in older children, the intestinal symptoms may be slight and discoverable only on specific investigation. I have had two patients with this disorder whose respiratory symptoms first brought them to notice at the ages of 12 and 14 years respectively, and who survived until the ages of 16 and nearly 20 years (Clinico-Pathological Conference, 1954). Another rare condition which must be thought of in patients with frequently recurrent attacks of pneumonia is agammaglobulinæmia (Citron, 1957). The infections associated with this condition have the characteristic that, although they are frequently recurrent, individually they may present no unusual feature, and most of them respond normally to appropriate antibacterial treatment.

In all these examples, it may be questioned whether the lung changes should be regarded as throwing light upon the systemic changes, or the systemic upon the pulmonary. In sarcoidosis and in those varieties of "honeycomb lungs" which are associated with systemic disorders, the usual situation is that the extrathoracic manifestations, if present, throw light upon the nature of the pulmonary changes. Thus in suspected sarcoidosis of the lungs, manifestations outside the lungs, especially in the skin, in the lymph nodes, the liver and the spleen, in the eyes and in the small bones of the hands, are sought in the attempt to establish the diagnosis. Similarly, in patients presenting the radiological picture of honeycomb lungs (Oswald and Parkinson, 1949), radiological evidence of eosinophilic granuloma of bones may rarely establish the diagnosis of the xanthomatous type, and the finding of adenoma sebaceum or subungual fibromata on physical examination indicates the mesodermal dysplasia type (Dawson, 1954). Both sarcoidosis and the xanthomatous type of honeycomb lung may be accompanied by diabetes insipidus (Spillane, 1952), though this is very rare, and in my small experience the obvious symptom of polyuria in cases of this sort has preceded the finding of the lung changes.

An important recent contribution to our knowledge of polyarteritis nodosa as it affects

the lungs was made by Rose and Spencer (1957), who defined a group of cases in which for a considerable period changes in the lungs may be the sole indication of what eventually will be a generalized disorder. In the course of a study of 111 cases of polyarteritis nodosa collected from 9 hospitals, Rose and Spencer were able to recognize a group of 32 in which the lungs were involved, and which presented important differences from the rest. A respiratory illness preceded the systemic changes, sometimes by a considerable interval. There was an eosinophilia of more than 1,500 per c.mm. in 54% of the "lung" cases, and in none of those without respiratory symptoms. The highest levels of eosinophilia were in the 12 patients who had asthma; these also had the longest period of respiratory illness before systemic generalization became apparent. The asthma had the distinctive feature that in no case was there a family history of asthma or hay fever. The "lung" group showed important histological differences from the other cases. These consisted of a higher incidence of granulomatous and necrotizing lesions, both in the arteries and unrelated to them, and more numerous eosinophils and giant cells in the polyarteritic lesions. 16% of the patients with lung involvement had granulomata in the nose or middle ear. The frequency of granulomata in the nose or middle ear and of granulomatous and necrotizing changes in the general histological picture indicates that the group of cases which has been described as Wegener's granulomatosis (Plummer *et al.*, 1956) should be considered as a special subdivision of polyarteritis nodosa. Whereas in the cases with lung involvement the sex ratio was equal, in those without lung involvement males outnumbered females by 1·6:1. The lung changes sometimes took the form of recurrent transient attacks of "pneumonia", and sometimes presented as chronic or unresolved consolidation. In 5 cases there were pleural effusions. Radiologically, the most frequent finding was consolidation of various sorts; there was a miliary type of shadowing in 3 cases, and evidence of cavitation in consolidated lung in 4. In the patients with initial pulmonary changes, systemic generalization, when eventually it occurred, usually led to rapid deterioration.

I have had 5 patients whose cases conform to the description by Rose and Spencer of the pulmonary variety of polyarteritis nodosa, and in whom the diagnosis has been proved, as well as several in whom I have made a clinical diagnosis, as yet unproved, in the pre-systemic stage. The following is a brief account of 3 of the proved cases.

*Case I.*—A man aged 55 developed paroxysmal cough, with dyspnœa. No abnormal physical signs were found, but in the chest X-ray a rather vague, fine reticular shadowing was observed. After nine months, he was referred to me. At this stage, the mottling in the lungs was somewhat denser, though still very fine. His liver had become palpable and there was some rise in the jugular venous pressure. He was admitted to hospital and rapidly went downhill with increasing enlargement of the liver, fever, pericarditis and albuminuria, and died in congestive heart failure. At necropsy, there were florid polyarteritic changes in the liver, kidneys and elsewhere, and healing polyarteritis in the pulmonary arteries. (This case has previously been reported briefly in 1956, *Brit. J. Radiol.*, **29**, 633.)

*Case II.*—This boy was first referred to me in 1948 when he was aged 11, because some rather nondescript shadows had been observed at the apices of the lungs, especially the right. He was rather under-sized for his age but no abnormal physical signs were found. All investigations were negative. Although the appearances were suggestive of pulmonary tuberculosis, tubercle bacilli were never found, and the skin failed to react to tuberculin. Over the years there was some slight increase in the shadowing at the apices until in 1954 a cavity appeared in the consolidated area at the right apex (Fig. 1). The appearances at this time so closely resembled those of pulmonary tuberculosis that in spite of the failure to find tubercle bacilli and his insensitivity to tuberculin, antibacterial treatment was given for several months; it produced no effect. He remained free from symptoms apart from poor physical development. In July 1955, extension of the lung shadows was observed at a routine examination, though there were no new symptoms (Fig. 2). A month later, he suddenly became ill with abdominal pain and fever, and was admitted to hospital in his terminal illness. The heart rapidly enlarged, a gallop rhythm developed, albuminuria appeared and the bouts of abdominal pain, accompanied by the passage of blood in the stools and diarrhœa, continued. It was only at this stage of generalization that the clinical diagnosis of polyarteritis nodosa was made, but the administration of corticotrophin could not arrest the steady downhill course, and he died about two months from the first clinical evidence of generalization of the disease. At necropsy there was evidence of florid polyarteritis in nearly every organ except the lungs. In these the changes were those of carnification.

*Case III.*—A man aged 46 was quite well until 1952, when he had a small hæmoptysis. A chest radiograph at this time showed a round, partly calcified focus in the lower lobe of the right lung. In 1955, he suddenly became wheezy, with cough and sputum, needing two weeks' hospital treatment. About May 1957, the wheeziness recurred and cough and repeatedly blood-stained sputum developed. In August 1957 he became breathless even at rest, and a number of spots appeared on the hands, arms and forehead. In October 1957 when I first saw him, he was ill and febrile. There were scattered brownish-pink nodules up to 7 mm. diameter, some vesiculated, on the hands (Fig. 3) and over the elbows, and a few, less prominent, on the forehead, with a scaly erythemato-urticarial rash extending just above the wrists. Many rhonchi were heard all over both lungs. The blood pressure



FIG. 1 (*Case II*).—Radiograph of apex of right lung, May 18, 1954.

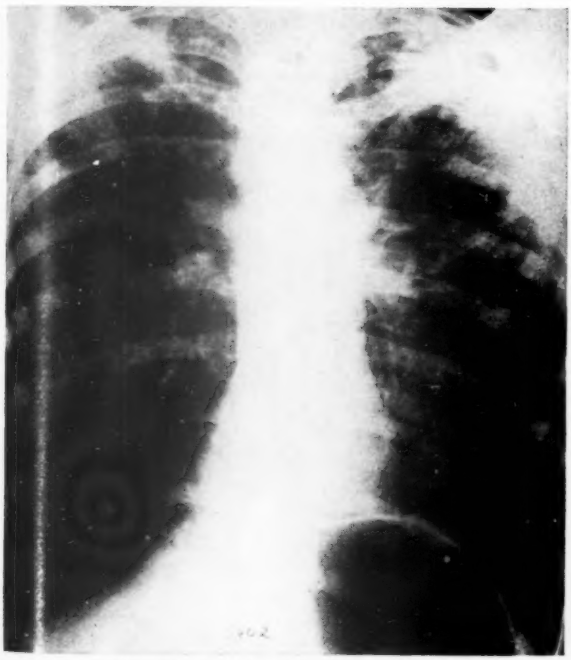


FIG. 2 (*Case II*).—Radiograph of chest, July 27, 1955.





FIG. 3 (*Case III*).—Left hand, to show skin lesions, October 1957.

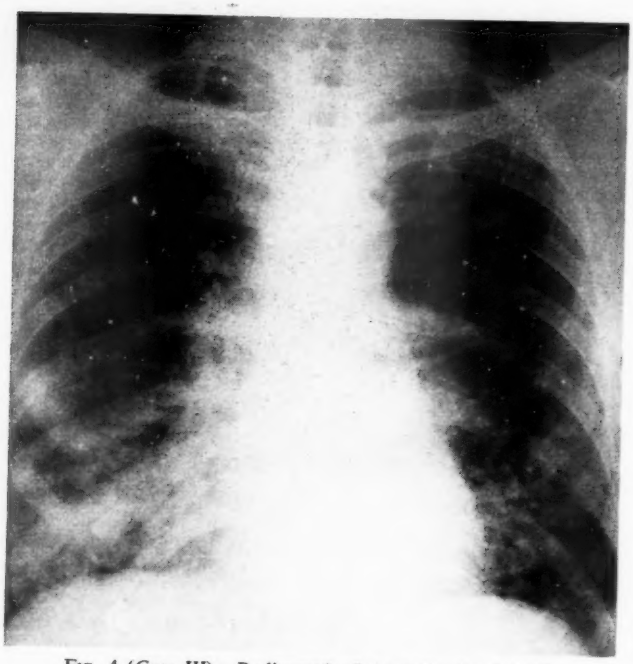


FIG. 4 (*Case III*).—Radiograph of chest, October 9, 1957.

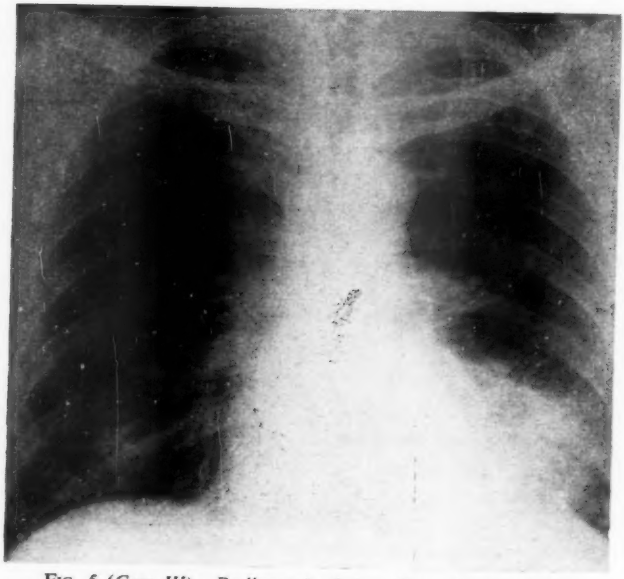


FIG. 5 (*Case III*).—Radiograph of chest, December 13, 1957.

was 120/80. Urine contained a trace of albumin. Blood count showed 19,000 leucocytes per c.mm., of which 5,500 were eosinophils. No L.E. cells were seen. The E.S.R. was 135 mm. (Westergren). A chest radiograph (Fig. 4) showed patchy coarse mottling throughout both lungs, especially at the bases. No evidence of sensitivity to the commoner inhalant allergens was found by dermal or bronchial sensitivity tests. A biopsy of a nodule from the right ring finger showed small granulomas with fibrinoid necrosis of collagen. There was no response to the administration of antibiotics, but prednisolone, 40 mg. daily, caused rapid clearing of the lung shadows and of the skin lesions and a fall in the E.S.R. to 40 mm.; but albuminuria increased and the blood urea rose to 79 mg. per 100 ml. The prednisolone was increased to 60 mg. daily. Although the E.S.R. fell to 16 mm., and the blood urea to 37 mg., albuminuria, 1 to 2 g. daily, continued. In December, he developed paræsthesiæ in the legs, suggestive of peripheral neuropathy. At present any reduction of the dose of prednisolone below 55 mg. daily results in exacerbation of his various symptoms. Consolidation of part of the left lower lobe consequent upon such a reduction is shown in Fig. 5; it resolved on restoration of the dose of prednisolone to its former level.

Although the diagnosis of the pre-systemic stage of polyarteritis nodosa is speculative, it may be suspected in patients who have asthma developing for the first time in adult life, with no family history of allergic disorders, with a high eosinophilia, and with persistent or recurrent consolidations in the lung which do not appear to be due to bacterial or other infection. The important differential diagnosis of such cases is from the allergic variety of pulmonary aspergillosis (Hinson *et al.*, 1952), but this condition is diagnosable by the finding of the aspergillus in the sputum, sometimes by bronchoscopy, and by the detection of sensitivity to aspergillus antigens. Once this possibility has been excluded, a patient presenting with the clinical picture described should probably be treated with corticosteroids on the provisional diagnosis of pulmonary polyarteritis, a careful watch being kept constantly for possible systemic generalization.

A rare syndrome, described by Parkin *et al.* (1955), from the Mayo Clinic, as necrotizing pulmonary alveolitis with acute glomerulonephritis, has certain affinities with the pulmonary form of polyarteritis nodosa, although it is clear that it affects vessels of much smaller calibre. It is germane to our present discussion because the pulmonary changes may precede by a considerable interval the rapidly advancing renal changes. I can best describe this syndrome by recounting the case of a patient who was recently under my care.

*Case IV.*—A man aged 29, previously healthy, developed slight cough and produced some blood-streaked sputum in August 1955. The hæmoptysis was repeated on several occasions and several chest X-rays were taken, but no abnormality was observed until November 1955, when a rather vague opacity of mottled character was observed in the middle zone of the right lung. Small hæmoptyses recurred from time to time, and the hæmoglobin fell to 66%. I first saw him in May 1956; the tip of the spleen was just palpable on deep inspiration, and for the first time a moderate albuminuria with cellular casts was observed. The hæmoglobin had risen to 84%, the leucocyte count was 9,000 with a normal differential count, the eosinophils amounting to 3%. The E.S.R. was 23 mm. in the first hour (Westergren). No L.E. cells were seen. The blood urea was 53 mg. per 100 ml. It was thought justifiable to carry out a lung biopsy in order to establish the diagnosis. The lung felt and looked normal. The biopsy showed interstitial hæmorrhage with hæmosiderin-containing macrophages in the alveoli. No changes were observed in the larger blood vessels. In spite of the administration of corticosteroids his course was rapidly downhill, the blood urea rising steeply with profuse albuminuria and oliguria, and eventually death with uræmia in July 1956. Hypertension developed in the last week or so of life. At necropsy there was evidence of severe glomerulonephritis with hyalinization and destruction of many glomeruli.

The lung changes in this syndrome present an interesting similarity to those of idiopathic hæmosiderosis, in which the lungs alone are affected. Indeed, I thought at first that my case fell into this category. It may be relevant to the pathogenesis of the syndrome that Eisen *et al.* (1950) showed that in rats an anti-lung serum localized selectively in the lungs and in the kidneys and that in the kidneys it localized mainly in glomeruli. Our concepts of these obscure syndromes—as of the so-called collagen diseases and of "idiopathic" interstitial fibrosis of the lungs—are unlikely to be clarified satisfactorily until we can analyse them by specific ætiological factors.

## REFERENCES


Bodian, M. (1952) Fibrocystic Disease of the Pancreas. London.
Citron, K. M. (1957) *Brit. med. J.*, i, 1148.
Clinico-Pathological Conference (1954) *Postgrad. med. J.*, **30**, 646.
Dawson, J. (1954) *Quart. J. Med.*, **23**, 113.
Eisen, H. N., Sherman, B., and Pressman, D. (1950) *J. Immunol.*, **65**, 543.
Hinson, K. F. W., Moon, A. J., and Plummer, N. S. (1952) *Thorax*, **7**, 317.
Meiss, J. V. (1954) *Amer. J. Obstet. Gynec.*, **67**, 962.
——, and Cass, J. W. (1937) *Amer. J. Obstet. Gynec.*, **33**, 249.
Oswald, N., and Parkinson, T. (1949) *Quart. J. Med.*, **18**, 1.
Parkin, T. W., Rusted, I. E., Burchell, H. B., and Edwards, J. E. (1955) *Amer. J. Med.*, **18**, 220.
Plummer, N. S., Angel, J. H., Shaw, D. B., and Hinson, K. F. W. (1956) *Thorax*, **12**, 57.
Ross, G. A., and Spencer, H. (1957) *Quart. J. Med.*, **26**, 43.
Spillane, J. D. (1952) *Thorax*, **7**, 134.

**Dr. Philip Ellman** (London):

This discussion goes beyond the boundaries of any specialty and serves to illustrate the inherent "wholeness" of medicine.

The implication of changing patterns of disease and changing forms of treatment must be remembered, in that the widespread and sometimes indiscriminate use of the newer antibiotic and other drugs (for example, the hydrallazine and hexamethonium compounds used for hypertension) may be hazardous and a factor in the apparent increase of diffuse interstitial fibrosis of uncertain ætiology, and of some collagen diseases.

I propose to concentrate on the pulmonary manifestations of the systemic collagen diseases, or, as I prefer to describe them, "connective tissue diseases". In these I shall include systemic lupus erythematosus, polyarteritis nodosa, scleroderma, dermatomyositis, "rheumatoid disease" and Sjögren's syndrome.

The collagen diseases appear to share some unifying principle based on an assumed common allergic ætiology; indeed, the role of hypersensitivity is at present a subject for investigation. The similarity of the histopathology, the merging patterns of these diseases one into another—for example, rheumatoid disease and polyarteritis, rheumatoid and Sjögren's disease with scleroderma—the vascular pathology founded upon an apparently uniform and diffuse arteritis, together with certain common clinical manifestations, are of considerable interest.

Noteworthy in these diffuse systemic connective tissue disorders are the allied pleural and pulmonary manifestations which may vary from dry and wet pleurisy, partial consolidation, widespread reticulation, and miliary mottling to chronic fibrosis and sclerocystic lung disease. The symptoms associated with acute progressive interstitial fibrosis of the lungs, which occurs in the so-called Hamman-Rich syndrome, and the possibility that this may not necessarily be a limited pulmonary disease, raises the question of a relationship with the connective tissue diseases, including the rheumatoid group. Certain analogous lesions with a similar lung tissue reaction may be found in the lungs and pleura and suggest a chronic interstitial form of the acute Hamman-Rich syndrome. The characteristic diffuse interstitial, fibrosing pneumonia is believed by certain workers, notably Rubin and Lubliner (1957), to resemble the type of tissue reaction (especially in the more chronic form of the disease) of certain of the so-called "rheumatoid group of collagen diseases".

*The Pleural and Pulmonary Lesions of Systemic Lupus Erythematosus*

Pleural lesions, both dry and wet and usually persistent, are quite common and may be the presenting feature. The effusions are usually small, although in one of my cases it was acute and massive. Pure lupus pulmonary lesions, although unusual, do occur and were present in 5 out of 12 of my cases of which 9 had, at one time or another, pleural involvement. Various types of lung parenchymal involvement have been observed and may occasionally dominate the clinical picture.

The lung changes are not specific and true focal allergic reactions must be carefully differentiated from secondary bacterial pulmonary infections which may complicate the terminal stages of the disease. The lesions may be pneumonic, patchy, and bronchopneumonic and are frequently basal in distribution. Plate-like atelectasis with elevation and fixation of the diaphragm on one or both sides has occurred in 3 of my 5 pulmonary cases. A chronic interstitial fibrosis dependent on a diffuse arteritis has been known and may possibly be related to the Hamman-Rich syndrome. The acute cases are the most likely to exhibit the characteristic L.E. cells in the peripheral blood or marrow and in one of my cases it was found in the effusion.

*The Lungs in Polyarteritis Nodosa*

Although this disease was described almost a century ago by Kussmaul and Maier (1866) it is little more than ten years since it was diagnosed clinically. Rose and Spencer (1957) have, in fact, reported on 111 histologically proven cases during a period of seven years. The diagnosis was made in life in about half of the cases. Their classification was based on the presence or absence of pulmonary involvement. Evidence of specific lung lesions, not unlike those of pulmonary tuberculosis, was found in one-third of the cases, which coincides with my own more limited series (Ellman and Cudkowicz, 1954; Ellman, 1956). The cases presenting with a respiratory illness, i.e. the group classified as pulmonary polyarteritis nodosa, usually present with three main types of illness, viz. bronchitic, asthmatic, pneumonic or bronchopneumonic. This respiratory illness may persist for weeks, months or years before the systemic manifestations of the disease ensue and occasionally these also may be confined to the respiratory system.

The lungs may show pathologically (Spencer, 1957) both necrotizing and granulomatous lesions which may cavitate and simulate tuberculous lesions. The pulmonary cases, moreover, may manifest certain features not characteristic of polyarteritis as a whole. These

are generally associated with high blood eosinophilia and occasionally granulomata in the upper air passages, especially the nose, and with lesions in the kidney. Klinge (1933) and Wegener (1936) have reported this combination of necrotizing granulomatous lesions and I have recently had under my care a case of "Wegener's granulomatosis". This presented with an upper respiratory tract malignant granulomatous lesion, associated with salivary and lacrimal lesions, both of which responded dramatically to local radiotherapy. Later, a lung lesion developed with a massive pericardial effusion and responded in the same way to X-ray therapy. Subsequent renal and systemic involvement responded well to steroid and antibiotic therapy but ensuing complications unfortunately led to death. A case from my series illustrating the pulmonary polyarteritis nodosa group is here briefly described:

*Case 1.*— Housewife, aged 40, complained of polyarthralgia and polymyalgia of several years' duration. She had had left-sided pleurisy in 1951. She was admitted to sanatorium in September 1955, following influenza, as a case of acute pulmonary tuberculosis with radiological evidence of infiltration and cavitation in the left upper zone, the infiltration extending into the left middle zone. In view of the acute lesion, she was immediately put on a course of daily streptomycin, 1 gram, and PAS, 20 grams, without any real improvement. The history showed that for the previous eighteen months she had had a cough with a little muco-purulent sputum as well as nocturnal wheezing for at least six months. Because of this wheezing, her husband insisted on her going to the chest clinic. I saw her in consultation after seven weeks of sanatorium treatment. The sputum was persistently negative for acid-fast bacilli and showed numerous eosinophils and Charcot-Leyden crystals. The blood count showed no anæmia, but a leucocytosis of 18,500 with 53% eosinophils. Electrophoresis of plasma proteins showed slight excess of gamma globulin. The Mantoux test was positive.

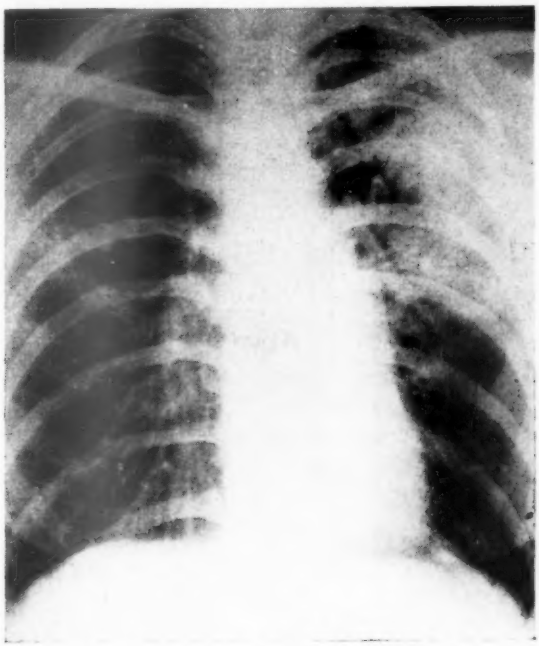


FIG. 1.—Pulmonary polyarteritis nodosa with infiltration and cavitation involving the left upper zone and extending to the left middle zone. This resolved with steroid therapy.

She was admitted to my chest unit. The blood eosinophilia persisted and although, apart from the polyarthralgia and myalgia, the lesion was confined to the lung, I regarded this as a case of pulmonary polyarteritis (Fig. 1). The response to steroid therapy has been dramatic, producing relief of symptoms, almost complete resolution of the lung lesion and a remarkable fall in the eosinophilia.

*The systemic type of polyarteritis nodosa* shows a true disseminated necrotizing arteritic lesion, frequently involving medium-sized arteries in many systems of the body, and the old term, periarteritis, is no longer applicable.

Clinically, the most common mode of onset is a pyrexia of unknown origin but the pleomorphic nature of the disease and its widespread symptomatology are now recognized.

While the disease may occur at any age, most often its onset is in early adult life. High fever, polymorphonuclear leucocytosis, a high sedimentation rate, polyarthralgia, polymyositis, polyneuritis, hypertension, renal disease, asthma and hæmorrhagic and other skin lesions are not uncommon manifestations, but, as Miller (1954) has emphasized, toxicity and multiple infarctions are the keynote of this disease, as illustrated by the following case:

*Case II.*—A 58-year-old physiotherapist had suffered five years previously from diarrhœa for one year. Investigations revealed nothing abnormal and the condition subsided spontaneously. For two years she had suffered from mild attacks of asthma, although not severe enough to require treatment. Six months before admission she suddenly developed generalized urticaria, with vomiting and diarrhœa. This again subsided spontaneously in one month. Three months later she developed polyarthralgia but when seen at our unit the only abnormality found was an E.S.R. of 30 mm. in one hour (Westergren). She was later admitted as an emergency with *acute abdominal pain*. A normal appendix was removed and, two weeks later, an acute inflamed gall bladder was excised. Section of the latter showed only eosinophilic infiltration. While convalescing from the operation she developed acute painful peripheral neuritis of her legs. Examination revealed a thin, pale woman with a low-grade pyrexia. Pulse was 98, blood pressure 200/90. The respiratory system was normal. She had a large, tender liver extending to the umbilicus. She had evidence of peripheral neuritis with sensory and motor changes involving both legs from the mid-calf downwards. A muscle biopsy confirmed the diagnosis of polyarteritis nodosa (Fig. 2). Her E.S.R. was 50 mm. in one hour (Westergren) and her blood count showed hæmoglobin 60%, and a white cell count of 14,900, with no eosinophilia. Soon, however, she developed a tachycardia of 140 and in the next few weeks transient lung shadows, showing areas varying from transient mottling, honeycombing, consolidation and, finally, a right-sided basal effusion (Fig. 3). Steroids were given, starting with ACTH and, later, prednisone. Initial response was good but she gradually deteriorated and finally succumbed. Post-mortem was refused. The pleomorphic nature of the condition is well illustrated in this case.



FIG. 2.—Muscle biopsy of calf showing fibrinoid necrosis with arteritis and small round cell infiltration.

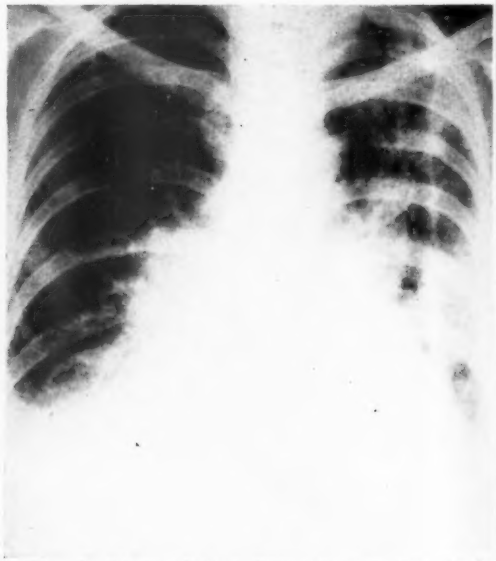


FIG. 3.—X-ray of chest from the same case showing scattered infiltration involving all zones of the left lung and a small right-sided basal effusion.

*Pulmonary Scleroderma*

Scleroderma may, for practical purposes, be divided into:

(1) localized scleroderma or morphœa,
(2) diffuse scleroderma,
(3) diffuse systemic sclerosis (acrosclerosis).

These groups are possibly related in the same way as discoid lupus is believed to be a localized manifestation of systemic lupus erythematosus. For the physician, however, the chief interest lies in the third group. It is usually preceded by a Raynaud phenomenon and,

indeed, a sympathectomy was done in two of my cases before the systemic sclerodermatous changes, more specifically the sclerodactylia, had developed. Involvement of the face, neck and upper trunk may then occur, with a characteristic facies, the skin over the face becoming tightened and drawn over the bony prominence. The hands have a characteristic appearance, with stiff flexed fingers, the tight skin bringing the joints into prominence to such an extent that they may resemble the rheumatoid hand, although the finger-tips often become shortened and blunted with disturbance of nail growth and absorption of bone of the terminal phalanges, ulceration of the skin and localized areas of calcification (calcinosis circumscripta). Vascular changes, with telangiectasia of the face, lips, tongue and hands, often occur. Sclerotic involvement of the œsophagus, heart, lungs, kidney and blood vessels may develop later.

Hypertension in the pulmonary circuit has been a feature of a few of my cases and all of them have shown a Raynaud phenomenon.

My cases of "pulmonary scleroderma" have presented with progressive dyspnœa, occurring mainly after the disease as a whole has been recognized. Sclerodactylia, some calcinosis and telangiectasis always occur before the heart and lungs become involved. Clinically, exertional dyspnœa, dry cough and reduction in vital capacity are the main features. Radiologically, diffuse pulmonary fibrosis and, in some cases, fine nodulation, fibrocystic (honeycomb) change and pleural fibrosis may be observed (Fig. 4). In one of my cases of dermatomyositis and scleroderma the lesions appeared to merge into each other.



FIG. 4.—Scleroderma of lungs showing diffuse pulmonary fibrosis with honeycombing and pleural fibrosis involving the middle and lower zones of both lungs.

*Dermatomyositis*

Dermatomyositis involves the skin, subcutaneous tissues and muscles, mainly in aged males, and as a general rule runs a chronic course. Rare and malignant complications of a pulmonary nature, sometimes involving breast or ovary in the female, are seen. In one of my scleroderma patients, a woman aged 42, dermatomyositis merged with it and a carcinoma of the breast was ultimately responsible for her demise.

*Pleural and Pulmonary Manifestations of Rheumatoid Disease*

"Rheumatoid disease" is a systemic disease whose principal local manifestation is arthritis. The systemic nature may be manifested by widespread pathological changes of mesenchymal connective tissue. These may occur in various tissues and organs, including the skin, with cutaneous and subcutaneous nodules, muscles, tendons, fascia, peripheral nerves, certain supporting structures including the synovia, pleura and pericardium and in some cases involving the viscera, e.g. the heart, lungs and spleen.

The study of the ocular effects, the refractory anæmia, the variant patterns of the disease, the merging of rheumatoid into other systemic collagen disease, the arterial pathology recorded by Cruickshank (1952, 1954), the lung pathology recorded by Christie (1954) and further clinical and pathological studies by Sinclair and Cruickshank (1956) and autopsy

studies by Cruickshank (1957), are all calculated to confirm our original viewpoint, now accepted by many authors, that the term "rheumatoid disease" (Ellman, 1947; Ellman and Ball, 1948) is more accurate and should be considered as a pathological entity (Cruickshank, 1957) in place of "rheumatoid arthritis". Since we described our first three cases of lung involvement in rheumatoid disease some 56 cases in all have been recorded (Edge and Rickards, 1957). Although we have seen many more cases than we have recorded, we would emphasize that these lung lesions are by no means common and should only be diagnosed after the most careful scrutiny.

The respiratory manifestations of rheumatoid disease that we have encountered can be classified as:

(1) Pleural lesions which may be (*a*) nodular, (*b*) diffuse (non-specific). The pleurisy may be dry or wet.

(2) Pulmonary lesions: (*a*) nodular, (*b*) diffuse (non-specific).

The nodular lesions in the lungs and pleura are almost identical histologically with those of the rheumatoid subcutaneous nodules, showing a central fibrinoid necrosis, surrounded by an encircling corona of closely-packed mesenchymal cells, the great majority of which are fibroblasts, external to which is a zone of inflammatory tissue (Collins, 1937). The interstitial changes at the periphery of the nodules closely resemble those of diffuse parenchymal lung lesions (Christie, 1954).

Experience suggests that the changes in the lungs or pleura (or both) may occur early or late in the rheumatoid process, and may be silent or symptomatic. The nodules can sometimes be demonstrated radiologically. The diffuse interstitial lesions show a reticular pattern. The diagnosis cannot really be made in the absence of arthritis and we would agree with Aronoff and his colleagues (1955) (who have found no example of "rheumatoid lung" in what they describe as a comparatively small group of patients) that the problem of differential diagnosis of lung lesions in rheumatoid arthritis can be most difficult. Nevertheless they found pleural adhesions in 27 out of 42 autopsies in "rheumatoid disease" as compared with 12 out of 42 in controls. Emerson (1956) describes 6 cases of pleural effusion in rheumatoid disease.

It is important to separate this apparently rare pulmonary condition from unrelated pulmonary disease, e.g. pulmonary tuberculosis, the pneumonias, sarcoidosis, carcinoma of the lung and the lung lesions in the systemic collagen diseases.

The rare occurrence of nodular lung and pleural lesions (Fig. 5) is generally accepted. We, like other workers, have also recorded interstitial lung changes, both at autopsy and during life, and the relationship of interstitial pulmonary fibrosis to "rheumatoid disease" has been studied by, among others, Rubin and Lubliner (1957). Using routine chest X-rays for all patients with rheumatoid disease, we have, on occasion, noted pleural effusions and

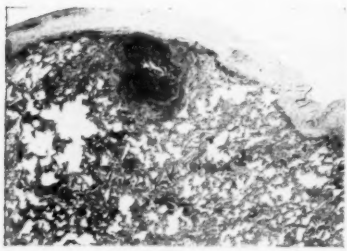


FIG. 5.—Photomicrograph of a section of the lung showing gross pleural thickening and a subpleural rheumatoid nodule radiating into the lung parenchyma and surrounded by fibrosis.

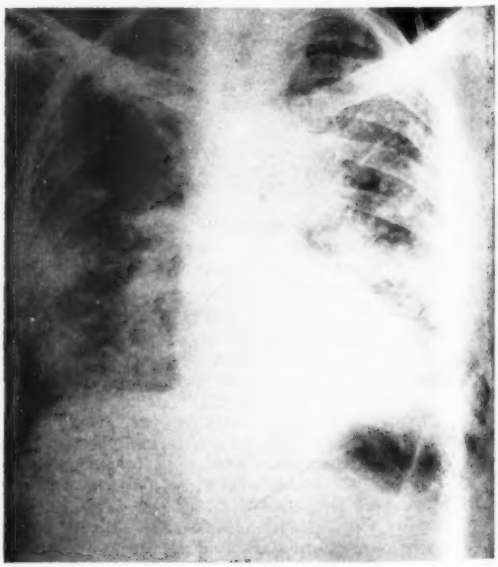


FIG. 6.—X-ray of chest showing widespread infiltration in all zones of both lungs. A further X-ray of the chest taken twelve months later showed appreciable resolution following steroid therapy. →

peripheral lung shadows which the closest possible clinical scrutiny has led us to regard as lung and pleural manifestations of rheumatoid disease. The non-specific interstitial lung changes may represent the end stages of acute lung lesions (Fig. 6) which at some stage in the patient's life may possibly have been of the nodular variety. Indeed, in view of the presumably asymptomatic nature of some of the pleural and pulmonary nodular lesions, we do not know how commonly these lesions occur nor what are the end-effects upon the adjacent lung in patients who have experienced lung remissions from the rheumatoid process. The nodular lung and pleural lesions (structurally indistinguishable from subcutaneous rheumatoid nodules) have been described by Bennett *et al.* (1940), Baggenstoss and Rosenberg (1941, 1943, 1944), Gruenwald (1948), Raven *et al.* (1948), Ellman *et al.* (1954), Christie (1954) and Spence (1955). Caplan (1953) described in coalminers a syndrome of nodular lung fibrosis associated in over 50% of the cases with rheumatoid arthritis.

Gough and his colleagues (1955), basing their work on extensive pathological studies, found that, in contrast with ordinary lungs, the pneumoconiotic lungs of coalminers appear exceptionally vulnerable to the rheumatoid process, sometimes more so than the joints. They have encountered lung lesions which seemed typical of the "rheumatoid pneumoconiotic type".

Christie (1954) has shown that rheumatoid disease affects the respiratory tract in the pleura (probably the commonest site), the bronchi, the pulmonary and bronchial vessels and the alveolar walls. The lesions he found in the lungs were as varied and widespread as those in other organs, and ranged from acute exudative foci to chronic scars of loose or dense texture. In size they varied from minute connective tissue buds to a giant nodule 7 cm. in diameter, structurally indistinguishable from the familiar subcutaneous rheumatoid nodule. Much of the fibrosis found by Christie was non-specific, although such areas usually contained more advanced foci, recognizable as rheumatoid nodules. It has been suggested that hypersensitivity may play a part in the production of this fibrosis.

In a series of 100 autopsies on patients who had suffered from rheumatoid disease, Cruickshank (1957) analysed the visceral lesions he had encountered. *They included 29 cardiac, 42 pleuritic and 6 pulmonary lesions. 20 out of 90 controls had pleural adhesions without apparent cause* (Sinclair and Cruickshank, 1956). Baggenstoss and Rosenberg (1944) found pleurisy in 22 out of 30 autopsies in "rheumatoid arthritis". Cruickshank found 6 examples of interstitial pneumonia although he has not yet studied these lungs in detail. All were, however, chronic and accompanied by diffuse or focal fibrosis. In contrast the incidence of interstitial pulmonary fibrosis in a series of 6,000 autopsies reviewed by Mallory (1948) was 16. "It thus seems likely that the association of interstitial pneumonia and fibrosis with 'rheumatoid disease' is more than coincidental" (Cruickshank, 1957). Whilst it is appreciated that this is a somewhat controversial subject, *the incidence of non-specific pleural and pulmonary lesions already noted, compared with that occurring in the non-rheumatoid subject, is surely clinically significant and can hardly be regarded as a chance finding.*

The lung changes in rheumatoid disease may be modified by other lesions present in the lung. For example, Caplan (1953) observed that in coalminers with rheumatoid disease the radiological pulmonary changes differed from those of miners without rheumatoid disease. The characteristic shadows were multiple, rounded, well defined and fairly evenly distributed throughout both lung fields, especially at the periphery.

Lodge (1956), in a radiological survey of 40 rheumatoid patients, found lung changes of some kind in 9 but he recognized that they might not be a true representation of the incidence of lung shadows in rheumatoid disease.

Price and Skelton (1956) have reported a case of rheumatoid arthritis with focal lesions where histologically focal arteritis and bronchiolitis had been found.

A review of the literature on the pulmonary manifestations of rheumatoid disease and a record of some of our cases have been given elsewhere (Ellman and Ball, 1948; Ellman and Cudkowicz, 1954; Ellman, 1956). We will merely record here 2 cases, one of a pleural effusion with specific lung and pleural nodules, and the other a case of a non-specific lung lesion.

*Case III.*—Male, aged 63, had had rheumatoid joint disease for seventeen years with widespread rheumatoid nodules. The subcutaneous nodules involved the scalp, the left olecranon process, the ulnar borders of both forearms and the ischial tuberosities. A nodule was also present in the sclera. These lesions were all associated clinically, in addition to polyarthritis, with a left pleural effusion, heart block and Jacksonian epilepsy. The initial response to steroid therapy was satisfactory, the subcutaneous nodules showing signs of regression. Eventually, however, the patient succumbed, and came to autopsy. This showed the co-existence of the subcutaneous nodules with nodules on the sclera, dura mater, synovia, myocardium, all valves, pericardium, intima of the ascending part of the aorta, the lungs (Fig. 5) and pleura.

*Case IV.*—Male, aged 54, farm labourer. Ten years' history of transient polyarthritis. In April 1953 he had an acute exacerbation of the joint lesions which settled down after three months. In November of that year he developed an acute febrile illness, cough with severe breathlessness and flare-up of his joint lesions. There were widespread physical signs throughout both lungs and an

X-ray examination of his chest showed mottling of all zones of both lungs (Fig. 6). There was no response to antibiotics. All investigations for tubercle, carcinoma, sarcoid, &c., were negative. A lung biopsy was done for me by Mr. W. Cleland. The sections showed evidence of fibrosing pneumonitis (non-specific). Joint and lung lesions responded well to steroid therapy.

*Sjögren's Syndrome*

This syndrome, occurring mainly in women of middle age and certainly over thirty years, is characterized in its fully developed form by kerato-conjunctivitis sicca, rhinitis sicca, xerostomia and laryngitis sicca. Sometimes the bronchial mucosa is affected and there may be intermittent swelling of the lacrimal and salivary glands. In some cases there is an associated rheumatoid joint lesion. It is suggested that the lacrimal and salivary lesions are ætiologically related to the rheumatoid process and Holm (1949) and Reader *et al.* (1951) believe that the non-specific inflammatory lesions may occur in the lacrimal, salivary and respiratory tissue as well as in joints, skin, muscles, tendons and subcutaneous tissues.

The chronic inflammatory changes in the parotid glands may produce permanent enlargement, sclerosis or atrophy in irregular combination and similar changes may occur in other salivary and lacrimal glands, usually without enlargement. In the past many such cases have been labelled Mikulicz's syndrome.

In one of our cases (Ellman *et al.*, 1951) the dryness of the bronchial mucosa was eventually fatal. The post-mortem histological examination confirmed that the pathological basis of the dryness of the mucous membranes (in some cases also of the skin) arises from chronic inflammatory atrophy of unknown cause, involving the salivary, lacrimal, mucosal and sweat glands. Post-mortem observations on such cases have been recorded by Sjögren (1933), Holm (1949), Ellman *et al.* (1951), Haas (1951), Reader *et al.* (1951), Morgan and Raven (1952) and Cardell and Gurling (1954).

The fundamental pathological features appear to be:

(*a*) Atrophy of certain glands, especially the lacrimal, salivary and submucous glands of the respiratory tract (upper and lower) and œsophagus, with consequent dryness of their associated mucosa.

(*b*) Rheumatoid joint disease.

It is of interest that in 2 of the 10 recorded autopsies there was a generalized necrotizing arteritis, closely related to polyarteritis nodosa. It is, therefore, reasonable to suppose that Mikulicz's syndrome is a manifestation of Sjögren's syndrome and that it belongs to the ill-defined group of collagen diseases. Gurling (1953) has noted its association with Felty's syndrome and features of both, with splenomegaly, have been recorded by several observers. Gurling also points to the disturbance of collagen and reticulo-endothelial tissues.

The presence at autopsy, in our case and in 1 of the 3 recorded by Cardell and Gurling, of a lipoid pneumonia involving the right middle lobe, is consistent with the use of oily nasal drops for the lubrication of the upper air passages.

The characteristic pathological dryness may give rise to obstruction in the parotid and salivary glands and in the respiratory tract, resulting in a secondary inflammatory granulomatous process and, possibly, suppuration. In our case the woman developed a bilateral dry basal pleurisy and later a basal pulmonary lesion not unlike a sarcoidosis.

I hope I have succeeded in indicating by a consideration of the pulmonary and pleural manifestations of some systemic connective tissue diseases, how disease in the lung can be an index of systemic disease.

## REFERENCES


Aronoff, A., Bywaters, E. G. L., and Fearnley, G. R. (1955) *Brit. med. J.*, ii, 228.

Baggenstoss, A. H., and Rosenberg, E. F. (1941) *Arch. intern. Med.*, **67,** 241.

——, —— (1943) *Arch. Path., Chicago*, **35,** 503.

——, —— (1944) *Arch. Path., Chicago*, **37,** 54.

Bennett, G. A., Zeller, J. W., and Bauer, W. (1940) *Arch. Path., Chicago*, **30,** 70.

Caplan, A. (1953) *Thorax*, **8,** 29.

Cardell, B. S., and Gurling, K. J. (1954) *J. Path. Bact.*, **68,** 137.

Christie, G. S. (1954) *Aust. Ann. Med.*, **3,** 49.

Collins, D. H. (1937) *J. Path. Bact.*, **45,** 97.

Cruickshank, B. (1952) *J. Path. Bact.*, **64,** 21.

—— (1954) *Ann. Rheum. Dis.*, **13,** 136.

—— (1957) *Proc. R. Soc. Med.*, **50,** 462.

Edge, J. R., and Rickards, A. G. (1957) *Thorax*, **12,** 352.

Ellman, P. (1947) *Proc. R. Soc. Med.*, **40,** 332.

—— (1956) *Postgrad. med. J.*, **32,** 370.

——, and Ball, R. E. (1948) *Brit. med. J.*, ii, 816.

——, and Cudkowicz, L. (1954) *Thorax*, **9,** 46.

——, ——, and Elwood, J. S. (1954) *J. clin. Path.*, **17,** 329.

——, Weber, F. P., and Goodier, T. E. W. (1951) *Quart. J. Med.*, **20,** 33.

Emerson, P. A. (1956) *Brit. med. J.*, i, 428.

GOUGH, J., RIVERS, D., and SEAL, R. M. E. (1955) *Thorax*, **10**, 9.
GRUENWALD, P. (1948) *Arch. Path., Chicago*, **46**, 59.
GURLING, K. J. (1953) *Ann. Rheum. Dis.*, **12**, 212.
HASS, E. (1951) *Virchows Arch.*, **320**, 264.
HOLM, S. (1949) *Acta ophthal. Kbh.*, Suppl. 33.
KLINGE, F. (1933) *Ergebn. allg. Path. path. Anat.*, **83**, 186.
KUSSMAUL, A., and MAIER, R. (1866) *Dtsch. Arch. klin. Med.*, **1**, 484.
LODGE, T. (1956) *Brit. J. Radiol.*, **29**, 645.
MALLORY, T. B. (1948) *Radiology*, **51**, 468.
MILLER, H. (1954) *Practitioner*, **173**, 133.
MORGAN, A. D., and RAVEN, R. W. (1952) *Brit. J. Surg.*, **40**, 154.
PRICE, T. H. L., and SKELTON, M. O. (1956) *Thorax*, **11**, 234.
RAVEN, R. W., WEBER, F. P., and PRICE, L. W. (1948) *Ann. Rheum. Dis.*, **7**, 63.
READER, S. R., WHYTE, H. M., and ELMES, P. C. (1951) *Ann. Rheum. Dis.*, **10**, 288.
ROSE, G. A., and SPENCER, H. (1957) *Quart. J. Med.*, N.S. **26**, 43.
RUBIN, E. H., and LUBLINER, R. (1957) *Medicine, Baltimore*, **36**, 397.
SINCLAIR, R. J. G., and CRUICKSHANK, B. (1956) *Quart. J. Med.*, N.S. **25**, 313.
SJÖGREN, H. (1933) *Acta ophthal. Kbh.*, Suppl. 2.
SPENCE, M. P. (1955) *Arch. Middx. Hosp.*, **5**, 95.
SPENCER, H. (1957) *Brit. J. Tuberc. Dis. Chest.*, **51**, 123.
WEGENER, F. (1936) *Verh. dtsch. path. Ges.*, **29**, 202 (publ. 1937).

**Dr. A. G. Heppleston** (Cardiff):

The topic concerns those systemic disorders in which lung changes may be the presenting or the predominating feature and, in a field so large, emphasis will be laid on conditions which have been the subjects of recent pathological investigation.

## "COLLAGEN" DISEASES

Connective tissues possess only four basic ways of reacting to injury: mucoid swelling of the ground substance, fibrinoid necrosis, cellular proliferation and fibrosis, or a combination of these changes. Fibrinoid necrosis of collagen, however, is not specific for any one type of injury, occurring in a variety of dissimilar disease processes, some localized and others generalized. Since connective tissues have so restricted a repertoire of pathological reaction, Rich (1946–47) stressed the difficulties of differential diagnosis among the various "collagen" diseases and pointed out that in any one of them features may be found which usually characterize other members of the group. Pagel and Treip (1955), for instance, reported overlapping syndromes amongst the "collagen" diseases and for these intermediate forms suggested the term "viscero-cutaneous collagenoses", whilst Fisher (1957) discussed the association of polyarteritis nodosa with rheumatoid arthritis. Both in experimental animals and in man there is reason to believe that anaphylactic hypersensitivity constitutes one important pathogenetic mechanism in connective tissue diseases (Rich, 1946–47). Moreover, recent immunohistochemical studies, using Coon's fluorescent antibody technique, provide presumptive evidence of an immunological mechanism in polyarteritis nodosa (Mellors and Ortega, 1956), active rheumatic carditis, rheumatoid disease and systemic lupus erythematosus (Vazquez and Dixon, 1957). It must be stressed that, though this group of diseases shows striking pathological and pathogenetic similarities, the precise ætiological agent may well vary in different cases.

### *Rheumatoid Disease*

With the recognition of visceral lesions in association with rheumatoid arthritis, it became clear that the condition was really a systemic one with arthritis as only one of the manifestations. Before a pulmonary lesion can be accepted as being of rheumatoid type it must exhibit characteristic pathological features or, if these are non-specific, the lesion must be shown to have a greater prevalence in the rheumatoid as compared with the non-rheumatoid members of a sample population. The only condition yet known to fulfil both criteria is "Caplan's syndrome".

In 1953 Caplan drew attention to the greatly increased prevalence of massive fibrosis in Welsh coalminers with rheumatoid arthritis. About 25% of these men also had peculiar, rounded and fairly well-demarcated opacities in their lung radiographs. These discrete opacities are now known to represent *rheumatoid nodules*, which may coalesce into massive lesions. Surveying a defined mining population in the South Wales coalfield, Miall *et al.* (1953) confirmed the original observations and further established that, though both manifestations commonly develop together, typical X-ray changes in the lungs may antedate the arthritis by several years. In "rheumatoid" pneumoconiosis, therefore, the lung may for a long period be the sole index of a systemic disease. Furthermore, these nodules characteristically appear in crops and develop much more rapidly than infective pneumoconiosis in non-arthritic miners. A recent pathological study (Gough *et al.*, 1955) suggests

that rheumatoid nodules may be distinguished from silicotic nodules by the presence of wide concentric zones of necrotic collagen separated by bands of dust and by the occurrence of peripheral, crescent-shaped areas of active inflammation in relation to necrotic collagen. Kellgren (1952) regards rheumatoid disease as being essentially an inflammatory reaction to necrosis of normal or pathologically-produced collagen. It is, therefore, suggested that, for reasons unknown, coal workers with rheumatoid arthritis react abnormally to the collagen produced in infective pneumoconiosis, and the non-specific inflammatory reaction, sometimes occurring in the absence of tubercle bacilli, is believed to represent the rheumatoid component. Ultimately rheumatoid nodules may pursue several courses. They may cease to progress and remain in a stationary phase, or they may calcify. Other lesions, however, undergo cavitation, their necrotic centres being expectorated, though the sputum may be free from tubercle bacilli. Rheumatoid nodules have now been recognized in arthritic workers from other coalfields and in other industries with a dust hazard. Similar nodules, situated in the lung or pleura, may also be associated with rheumatoid arthritis in individuals without known occupational exposure to dust, but such instances are distinctly uncommon (Bennett *et al.*, 1940; Gruenwald, 1948; Raven *et al.*, 1948; Bevans *et al.*, 1954; Christie, 1954; Ellman *et al.*, 1954; Maher, 1954; Skogrand, 1956).

*Non-specific fibrosis* of the lungs also occurs in combination with rheumatoid disease (Edge and Rickards, 1957). Sometimes the fibrosis is of diffuse interstitial type (Ellman and Ball, 1948; Katz and Auerbach, 1951; Rubin, 1955), reminiscent of that described by Hamman and Rich. The pathological evidence suggests that, whatever the precise cause, interstitial fibrosis may develop on the basis of a fibrinous intra-alveolar exudate, which, when limited in amount, becomes applied to the alveolar walls under the forces of respiration and then undergoes organization. This is a possible sequence of events in isolated diffuse interstitial fibrosis (Heppleston, 1951). Patchy fibrinous pneumonia has been observed in rheumatoid disease (Christie, 1954) and in other instances of this condition the lungs have shown vascular lesions (Ellman and Ball, 1948; Christie, 1954; Price and Skelton, 1956), which might account for fibrinous exudation. A similar process of organization may also operate in rheumatic pneumonitis, starting with a necrotizing angiitis and focal necroses of alveolar walls (Gouley, 1938; Neuberger *et al.*, 1944; Seldin *et al.*, 1947) and progressing to diffuse interstitial fibrosis (Gouley, 1938). Rich (1946–47) stressed the anaphylactic nature of the migratory pneumonitis of rheumatic fever. Although these examples suggest that occasionally connective tissue disease accounts for diffuse interstitial fibrosis, this condition usually occurs alone and its features are non-specific. A chance association between diffuse interstitial fibrosis and rheumatoid disease cannot therefore be excluded at present.

*Honeycomb lung*, which possesses certain pathological affinities with interstitial fibrosis, has also occurred in combination with rheumatoid arthritis (Dixon and Ball, 1957) but as yet the association can only be regarded as coincidental.

The pulmonary lesions of rheumatoid disease occurring in the non-industrial population are seen in their correct perspective when it is recalled that no specific lung lesions were observed in a series of 130 cases examined radiologically (Aronoff *et al.*, 1955) and that none was found at autopsy in a total of 88 cases reported by three separate groups of observers (Rosenberg *et al.*, 1944; Aronoff *et al.*, 1955; Sinclair and Cruickshank, 1956).

*Necrotizing Angiitis*

Zeek's classification is now widely adopted (Zeek, 1952; Knowles *et al.*, 1953). Reference has already been made to the necrotizing vascular lesions of *rheumatic fever* and *rheumatoid disease*, which most likely fall into the category of hypersensitivity angiitis. Regarding *polyarteritis nodosa*, Zeek distinguishes primary and secondary types, the latter being a sequel of pulmonary hypertension. Both forms are characterized by an initial fibrinoid necrosis with a subsequent inflammatory reaction. It is clear from Rose and Spencer's (1957) recent analysis of a large series of cases of primary polyarteritis nodosa, that a respiratory illness not uncommonly precedes evidence of polyarteritis, perhaps by years. Pulmonary involvement takes the form of a necrotizing granulomatous lesion in addition to fibrinoid necrosis of capillaries and to the arteritis which tends to affect bronchial more than pulmonary vessels. Some cases in this series also had a necrotizing glomerulitis and a few had nasal granulomata, suggesting a relationship to *Wegener's granulomatosis*. Walton and Leggat (1956) suggest that Wegener's disease commences with a necrotizing granulomatous lesion, possibly of infective or allergic origin, in the upper or lower respiratory tract. Hypersensitivity is then believed to develop either to bacterial or tissue breakdown products or to drugs, with disseminated angiitis, glomerulonephritis and granulomata as consequences. It now appears that *malignant granuloma of the nose* may occasionally be the first manifestation of a systemic condition indistinguishable from Wegener's syndrome (Singh *et al.*, 1958).

*Systemic Lupus Erythematosus*

This condition is sometimes characterized by a remarkable waxing and waning pneumonitis (Klemperer *et al.*, 1941), which Rich (1946–47) regarded as being of anaphylactic type. As a rule, however, the pathological changes in the lung are disappointing. For instance, Purnell *et al.* (1955) found no pathognomonic pulmonary lesions in a series of 54 necropsies and the experience of Cordasco *et al.* (1957) was similar. The so-called basophilic mucinous œdema of the pulmonary connective tissues (Baggenstoss, 1952) is not always an impressive feature, but fibrinoid necrosis of vessels may be seen.

*Scleroderma* (Progressive systemic sclerosis)

Pulmonary involvement is a well-recognized feature of scleroderma and derives its importance from the fact that lung changes may antedate the onset of typical skin lesions (Lloyd and Tonkin, 1948; Shuford *et al.*, 1953; Mahrer *et al.*, 1954). The pulmonary manifestations take several forms. Widespread fibrosis of alveolar walls has been described in a few instances (Getzowa, 1945; Shuford *et al.*, 1953; Mahrer *et al.*, 1954). Fibrous nodules or extensive areas of solid fibrosis also occur. Perhaps the most interesting lesion is honeycomb lung, in which cysts are set in mature collagenous tissue. Both solid fibrosis and fibrocystic change may be encountered in different parts of the same lung. Getzowa (1945) suggested that the primary pulmonary lesion in scleroderma was diffuse fibrosis of alveolar walls but too few early examples are yet on record to be certain. Obliterative vascular lesions, sometimes with fibrinoid, have also been regarded as the initial change, but they could equally be secondary to parenchymal damage. The distribution and features of the lung lesions hardly suggest that they are caused by occlusion of bronchial arteries, as Ellman and Cudkowicz (1954) tended to believe. The idea that pulmonary fibrosis in scleroderma is a consequence of aspiration pneumonia due to œsophageal involvement is no longer tenable. Mahrer *et al.* (1954) encountered several instances of scleroderma with pulmonary fibrosis but without œsophageal disease. Furthermore, the occurrence of densely fibrous areas towards the apex of the lung is not consistent with the aspiration hypothesis.

## Sarcoidosis

Pulmonary involvement is a common occurrence in sarcoidosis. Respiratory symptoms frequently constitute the presenting feature (Scadding, 1956*a*) but the first indication of lung involvement may only be provided by radiological or even post-mortem examination. The basic lesion is the miliary granuloma, composed of epithelioid cells, giant cells and some lymphocytes; central fibrinoid change of restricted extent may be seen, but not caseation. Conchoidal and asteroid bodies are no longer regarded as specific features of sarcoid lesions.

Sarcoidosis of the lung assumes several pathological forms of which the disseminated *miliary* one is, perhaps, the best known. The discrete focal granulomata are not always evenly scattered throughout the lung, there being a tendency for them to cluster around bronchi and blood vessels and also subpleurally. When situated in alveolar walls the granulomata encroach on air spaces. Miliary lesions often coalesce and thereby give rise to a *nodular* form of the disease, whilst further extension of the same process leads to the development of large confluent *masses* in which fibrosis dominates the picture and gradually replaces the granulomatous element. Such masses may be seen in the upper and central parts of the lung or towards the hilum. Another factor may operate in the production of massive sarcoid lesions, namely collapse, for which bronchial stenosis, due to sarcoid involvement, is probably responsible (Longcope and Freiman, 1952; Citron and Scadding, 1957). A further manifestation of pulmonary sarcoidosis is *honeycomb* lung, in which typical granulomata may be found in the fibrous tissue separating the cysts. It is important to remember that occasionally pulmonary sarcoidosis so impedes the lesser circulation that right ventricular hypertrophy develops and death ensues in congestive heart failure (Ricker and Clark, 1949; Longcope and Freiman, 1952).

Finality has not yet been reached regarding the nature of the systemic sarcoid reaction. Pinner (1937) summarized the available evidence suggesting that sarcoidosis was a non-caseating form of tuberculosis and Scadding (1956*a*, *b*) has argued strongly in favour of a tuberculous origin for many British cases of sarcoidosis. A corollary to this concept is that sarcoidosis represents not a disease but a syndrome, that is a response sometimes provoked by tubercle bacilli, sometimes by beryllium dust and possibly by other means not yet identified (*Brit. med. J.*, 1957). The hyperglobulinæmia of sarcoidosis further suggests that an immune mechanism may sometimes be at work. It is of interest to find that from some sarcoid lesions it is possible to extract a mycolic acid which is chemically similar to that present in tubercle bacilli themselves (Nethercott and Strawbridge, 1956) even though viable bacilli cannot be recovered from these sarcoid lesions.

### Eosinophilic Granuloma

The term "eosinophilic granuloma" embraces three systemic conditions formerly described as separate entities, ranging from the rapidly progressive form (Letterer-Siwe disease), through the slowly progressive type (Hand-Schüller-Christian disease) to the relatively benign and often localized eosinophilic granuloma. Ætiological understanding of these conditions was aptly summarized by Lichtenstein (1953) when he gave them the collective designation of "histiocytosis X". Eosinophilic granuloma is known to involve extra-skeletal tissues, among them the lung (Thannhauser, 1950; Lichtenstein, 1953), and to become increasingly fibrous in the retrogressive or chronic phase (Engelbreth-Holm *et al.*, 1944). It appears that eosinophilic granuloma is sometimes confined to the lung and respiratory disturbances may be the first evidence of the disease. The acute generalized form may show both solid and cystic infiltrations of the lung by primitive cells. The granulomatous stage is characterized by scattered collections of histiocytes and eosinophils, whilst the lung between the granulomatous areas may undergo cystic change. Honeycomb lung is a recognized manifestation of the fibrous phase of eosinophilic granuloma (Heppleston, 1956).

### Tuberous Sclerosis

This is usually a generalized condition in which honeycomb lungs with smooth muscle hyperplasia and considerable interstitial fibrosis may occur (Berg and Vejlens, 1939; Samuelsen, 1942; Berg and Nordenskjöld, 1946; Dawson, 1954). Licht (1942), however, considered that pulmonary involvement might be the sole manifestation of this disease. I encountered one case of honeycomb lung as an isolated lesion in which smooth muscle hyperplasia was so pronounced as to constitute the essential pathological feature and warrant the term of leiomyomatosis (Heppleston, 1956). Only Rosendal's (1942) case seems to compare with this one and it is possible that both represent an unusual form of tuberous sclerosis. In the non-specific form of honeycomb lung muscle hyperplasia also occurs but it is much less severe than in leiomyomatosis and is associated with fibrosis and chronic inflammatory cell infiltration.

### The Main Types of Pathological Change Assumed by Systemic Conditions when they Affect the Lung

(1) *Exudation, infiltration or fibrosis of focal or patchy distribution.*—The underlying change may prove to be allergic pneumonia, rheumatoid disease, necrotizing arteritis, scleroderma, sarcoidosis, eosinophilic granuloma, reticuloses such as mycosis fungoides and Hodgkin's disease, or mucoviscidosis.

(2) *Massive fibrosis* usually represents a progression from localized fibrosis both by extension and by coalescence.

(3) *Diffuse interstitial fibrosis.*—Although most instances are of undetermined ætiology and show no specific features, it seems that "collagen" diseases, such as rheumatic fever, rheumatoid disease and scleroderma, may occasionally be responsible. The fibrinous pneumonitis associated with uræmia (Doniach, 1947) and with hexamethonium therapy (Morrison, 1953; Doniach *et al.*, 1954; Lansbury and Rogers, 1955) may be yet another cause of interstitial fibrosis of the lung, provided survival is sufficiently prolonged.

(4) *Fibrocystic change or honeycomb lung* (Heppleston, 1956).—This is believed to be an acquired condition, distinguishable on micro-anatomical grounds from congenital cystic disease. The essential feature is the obliteration by granulomata or fibrosis of certain bronchioles, respiratory and non-respiratory, together with their subdivisions. Unaffected bronchioles in the neighbourhood then appear to undergo compensatory dilatation, so forming cystic spaces in contiguity with consolidated or fibrotic areas. Progressive enlargement of the cysts seems to depend on secondary valvular obstruction of the bronchioles entering them.

The fibrous component of honeycomb lung evidently arises in several ways. Patchy interstitial fibrosis of alveolar walls can apparently be associated with cystic enlargement of air passages in adjacent areas of non-fibrosed lung and the interstitial fibrosis may merge with typical honeycomb lung. Fibrosis may also develop on the basis of organized bronchopneumonia, restricted areas of pulmonary collapse and certain specific granulomata such as sarcoidosis, eosinophilic granuloma and tuberculosis after streptomycin therapy.

### REFERENCES

Aronoff, A., Bywaters, E. G. L., and Fearnley, G. R. (1955) *Brit. med. J.*, ii, 228.
Baggenstoss, A. H. (1952) *Proc. Mayo Clin.*, **27**, 412.
Bennett, G. A., Zeller, J. W., and Bauer, W. (1940) *Arch. Path., Chicago*, **30**, 70.
Berg, G., and Nordenskjöld, A. (1946) *Acta med. scand.*, **125**, 428.
——, and Vejlens, G. (1939) *Acta pædiat., Stockh.*, **26**, 16.

BEVANS, M., NADELL, J., DEMARTINI, F., and RAGAN, C. (1954) *Amer. J. Med.*, **16,** 197.
*Brit. med. J.* (1957) ii, 634.
CAPLAN, A. (1953) *Thorax*, **8,** 29.
CHRISTIE, G. C. (1954) *Aust. Ann. Med.*, **3,** 49.
CITRON, K. M., and SCADDING, J. G. (1957) *Thorax*, **12,** 10.
CORDASCO, E. M., HASERICK, J. R., SKIRPAN, P. J., and VAN ORDSTRAND, H. S. (1957) *J. chron. Dis.*, **5,** 290.
DAWSON, J. (1954) *Quart. J. Med.*, N.S. **23,** 113.
DIXON, A. ST. J., and BALL, J. (1957) *Ann. Rheum. Dis.*, **16,** 241.
DONIACH, I. (1947) *Amer. J. Roentgenol.*, **58,** 620.
——, MORRISON, B., and STEINER, R. E. (1954) *Brit. Heart J.*, **16,** 101.
EDGE, J. R., and RICKARDS, A. G. (1957) *Thorax*, **12,** 352.
ELLMAN, P., and BALL, R. E. (1948) *Brit. med. J.*, ii, 816.
——, and CUDKOWICZ, L. (1954) *Thorax*, **9,** 46.
——, ——, and ELWOOD, J. S. (1954) *J. clin. Path.*, **7,** 239.
ENGELBRETH-HOLM, J., TEILUM, G., and CHRISTENSEN, E. (1944) *Acta med. scand.*, **118,** 292.
FISHER, E. R. (1957) *Amer. J. clin. Path.*, **27,** 191.
GETZOWA, S. (1945) *Arch. Path., Chicago*, **40,** 99.
GOUGH, J., RIVERS, D., and SEAL, R. M. E. (1955) *Thorax*, **10,** 9.
GOULEY, B. A. (1938) *Amer. J. med. Sci.*, **196,** 1.
GRUENWALD, P. (1948) *Arch. Path., Chicago*, **46,** 59.
HEPPLESTON, A. G. (1951) *Thorax*, **6,** 426.
—— (1956) *Thorax*, **11,** 77.
KATZ, H. L., and AUERBACH, O. (1951) *Dis. Chest.*, **20,** 366.
KELLGREN, J. H. (1952) *Brit. med. J.*, i, 1152.
KLEMPERER, P., POLLACK, A. D., and BAEHR, G. (1941), *Arch. Path., Chicago*, **32,** 569.
KNOWLES, H. C., ZEEK, P. M., and BLANKENHORN, M. A. (1953), *Arch. intern. Med.*, **92,** 789.
LANSBURY, J., and ROGERS, F. B. (1955) *Bull. rheum. Dis.*, **5,** 85.
LICHT, E. DE F. (1942) *Acta radiol., Stockh.*, **23,** 151.
LICHTENSTEIN, L. (1953) *Arch. Path., Chicago*, **56,** 84.
LLOYD, W. E., and TONKIN, R. D. (1948) *Thorax*, **3,** 241.
LONGCOPE, W. T., and FREIMAN, D. G. (1952) *Medicine, Baltimore*, **31,** 1.
MAHER, J. A. (1954) *Arch. Path., Chicago*, **58,** 354.
MAHRER, P. R., EVANS, J. A., and STEINBERG, I. (1954) *Ann. intern. Med.*, **40,** 92.
MELLORS, R. C., and ORTEGA, L. G. (1956) *Amer. J. Path.*, **32,** 455.
MIALL, W. E., CAPLAN, A., COCHRANE, A. L., KILPATRICK, G. S., and OLDHAM, P. D. (1953) *Brit. med. J.*, ii, 1231.
MORRISON, B. (1953) *Brit. med. J.*, i, 1291.
NETHERCOTT, S. E., and STRAWBRIDGE, W. G. (1956) *Lancet*, ii, 1132.
NEUBERGER, K. T., GEEVER, E. F., and RUTLEDGE, E. K. (1944) *Arch. Path., Chicago*, **37,** 1.
PAGEL, W., and TREIP, C. S. (1955) *J. clin. Path.*, **8,** 1.
PINNER, M. (1937) *Amer. Rev. Tuberc.*, **36,** 706.
PRICE, T. M. L., and SKELTON, M. O. (1956) *Thorax*, **11,** 234.
PURNELL, D. C., BAGGENSTOSS, A. H., and OLSEN, A. M. (1955) *Ann. intern. Med.*, **42,** 619.
RAVEN, R. W., WEBER, F. P., and PRICE, L. W. (1948) *Ann. Rheum. Dis.*, **7,** 63.
RICH, A. R. (1946–47) *Harvey Lect.*, **42,** 106.
RICKER, W., and CLARK, M. (1949) *Amer. J. clin. Path.*, **19,** 725.
ROSE, G. A., and SPENCER, H. (1957) *Quart. J. Med.*, N.S. **26,** 43.
ROSENBERG, E. F., BAGGENSTOSS, A. H., and HENCH, P. E. (1944) *Ann. intern. Med.*, **20,** 903.
ROSENDAL, T. (1942) *Acta radiol., Stockh.*, **23,** 138.
RUBIN, E. H. (1955) *Amer. J. Med.*, **19,** 569.
SAMUELSEN, E. (1942) *Acta radiol., Stockh.*, **23,** 373.
SCADDING, J. G. (1956*a*) *Proc. R. Soc. Med.*, **49,** 799.
—— (1956*b*) *Tubercle, Lond.*, **37,** 371.
SELDIN, D. W., KAPLAN, H. S., and BUNTING, H. (1947) *Ann. intern. Med.*, **26,** 496.
SELFORD, W. H., SEAMAN, W. B., and GOLDMAN, A. (1953) *Arch. intern. Med.*, **92,** 85.
SINCLAIR, R. J. G., and CRUICKSHANK, B. (1956) *Quart. J. Med.*, N.S. **25,** 313.
SINGH, M. M., STOKES, J. F., DRURY, R. A. B., and WALSHE, J. M. (1958) *Lancet*, i, 401.
SJOGRAND, A. (1956) *Acta rheum. scand.*, **2,** 17.
THANNHAUSER, S. J. (1950) Lipoidoses. 2nd ed. London; p. 408.
VAZQUEZ, J. J., and DIXON, F. J. (1957) *Lab. Invest.*, **6,** 205.
WALTON, E. W., and LEGGAT, P. O. (1956) *J. clin. Path.*, **9,** 31.
ZEEK, P. M. (1952) *Amer. J. clin. Path.*, **22,** 777.

## BOOKS RECEIVED FOR REVIEW

**Alston (J. M.)** and **Broom (J. C.).** Leptospirosis in man and animals. pp. xii+367. Edinburgh and London: Livingstone. 40s. 1958.

**Armstrong (J. R.).** Lumbar disc lesions. 2nd edit. pp. xii+244. Edinburgh and London: Livingstone. 45s. 1958.

**de Kok (W.).** You and your child. Revised edit. pp. vii+186. London: Pan Books. 2s. 6d. 1958.

**Gordon-Taylor (Sir G.),** and **Walls (E. W.).** Sir Charles Bell; his life and times. pp. xii+288. Edinburgh and London: Livingstone. 42s. 1958.

**Grumbach (A.),** and **Kikuth (W.),** eds. Die Infektionskrankheiten des Menschen und ihre Erreger. 2 vols. pp. xl+1702. Stuttgart: Thieme. DM.198. 1958.

**Hale (A. J.).** The interference microscope in biological research. pp. xi+114. Edinburgh and London: Livingstone. 20s. 1958.

**Hawkins (N. G.).** Medical sociology. pp. xx+290. Springfield, Ill.: Thomas. Oxford: Blackwell. 51s. 1958.

**Hosler (R. M.).** A manual on cardiac resuscitation. 2nd edit. pp. xx+208. Springfield, Ill.: Thomas. Oxford: Blackwell. 42s. 1958.

**Keevil (J. J.).** Medicine and the Navy, 1200–1900. Vol. II, 1649–1714. pp. 331. Edinburgh and London: Livingstone. 40s. 1958.

**Peeters (H.),** ed. Protides of the biological fluids: Proceedings of the 5th Colloquium, Bruges 1957. pp. viii+260. London: Cleaver-Hume. Amsterdam, etc.: Elsevier. 45s. 1958.

**Raven (R. W.),** ed. Cancer. Vol. 3: pp. viii+483+18. London: Butterworth. 85s. 1958.

**Richardson (R. G.).** The surgeon's tale. pp. 256. London: George Allen and Unwin. 25s. 1958.

**Rob (C.),** and **Smith (R.),** eds. Operative surgery (in 8 vols.). Vol. 7: Breast, genito-urinary system. pp. xii+273+3. London: Butterworth. £5 10s. 1958.

**Rob (C.),** and **Smith (R.),** eds. Operative surgery (in 8 vols.). Vol. 8: Neuro-surgery, eyes, ear, nose and throat. London: Butterworth. £5 10s. 1958.

**Shy (G. M.), Bradley (R. B.),** and **Matthews (W. B.).** External collimation detection of intracranial neoplasia with unstable nuclides. pp. vii+144. Edinburgh and London: Livingstone. 30s. 1958.

**Stallard (H. B.).** Eye surgery. 3rd edit. pp. xii+899. Bristol: Wright. 95s. 1958.

**Transactions of the American Ophthalmological Society.** 1957. Vol. LV. pp. xvii+805. Columbia University Press. London: Oxford University Press. 144s. 1958.

**Trelease (S. F.).** How to write scientific and technical papers. pp. xii+185. London: Baillière, Tindall & Cox. 26s. 1958.

**Whittington (T. H.).** The art of clinical refraction. pp. vi+286+vii. London: Oxford University Press. 30s. 1958.

**Wyburn-Mason (R.).** The reticulo-endothelial system in growth and tumour formation. pp. 206. London: Kimpton. 42s. 1958.

# Section of General Practice

President—G. M. KERR, M.B., L.R.C.P., F.F.A. R.C.S.

[*April* 16, 1958]

## DISCUSSION ON MANAGEMENT OF PRACTICE

**Dr. H. G. Barnes** (Cullercoats, North Shields):

### *Practice in an Industrial Area*

My practice is mixed; about two-thirds is industrial and one-third is suburban. It is situated in Tynemouth, the total population of which is 67,000. Professional and business people tend to live in suburban Tynemouth, the skilled artisans live chiefly in the newer housing estates, and the unskilled tend to live in the old dirty streets, so typical of the industrial revolution, of North Shields. There are also two separate pre-war housing estates, and two excellent post-war building estates. The chief employment is in shipbuilding and ship-repairing, heavy and light engineering, the fishing industry, coal-mining and at the smaller factories on the trading estate.

*Practice Organization*

The practice is about 8,400 and is shared by 3 partners. Its area is about 4 miles long and 1 mile in depth, extending along the north bank of the Tyne. The whole essence of our practice is that work and patients are shared and we regard ourselves as an integrated whole, rather than three separate units under one roof. Our problem is to organize ourselves to cope with a fairly large amount of morbidity; to organize our work so that our services to our patients are given without loss of medical efficiency.

We have two surgeries about one and a half miles apart. The first is in the residential area of Tynemouth and is attached to a partner's house. At North Shields we cater for the industrial area and the housing estates. Here we have two consultation rooms outside of which is a small waiting area for feeding both rooms, and the receptionist's office; upstairs, rather inconveniently, the waiting room. This building is looked after by the caretakers, who are responsible for cleaning and for the majority of telephone messages, and who act as receptionists during holidays and illnesses.

We employ one receptionist, who has been trained in many duties. During surgery she obtains the record cards which are kept in her office in metal filing cabinets. Time is saved by repeat prescriptions, certificates, requests for ambulance transport, &c., being completed by the receptionist, and then signed by the doctor. She is also trained in sterilizing the syringes and instruments, keeping our visiting bags and the communal midwifery bag at full strength, testing urines, reading E.S.R.s and hæmoglobins, and generally keeping all our documents in order. At the end of the week she enters only important illnesses on the records of those patients being visited, in conjunction with the doctor. Our efficiency and speed of work depend a great deal on her. We are fairly prompt about our consultation hours, closing the doors at the advertised time. Consequently we have very few latecomers. In both surgeries time is saved by a buzzer system for calling patients.

We hold an antenatal clinic once a week—this is now in its eighth year. A maternity record is made out of a continuation card, and this is inserted in the record card after the postnatal examination. We share surgery times so that each doctor holds 9 surgery sessions per week; each doctor has one half-day per week. The patients know by notices displayed, and by experience, which partner is available for consultation and when. We have our own rota system within the practice, and do not belong to a rota for Sunday duty organized by other practices in the area. One partner has one week on duty during which period he does all the extra calls 'phoned in after morning surgery, all the night calls, and all the midwifery. The following week he recuperates and copes with the extra number of visits he has collected. The third week he is on second call for anæsthetics, and help if the duty doctor requires it. Visits are divided between us after morning surgery, equally, and allowing for requests by patients to be visited by the doctor for whom they may ask.

*A Typical Day in the Practice*

I usually start about 8.15 a.m. with visits to patients in hospital. Incidentally we have open access here to the X-ray, Pathology and ECG departments; or I may visit confinement cases in the three small G.P. maternity units; or I may give an injection to a patient with whom I have made a previous arrangement. Time is saved here by issuing the patient with his own syringe and instructing him in its sterilization and preparation. Morning surgery

begins at 9.0 a.m. and is over about 10.30 a.m. Coffee follows surgery—the morning's mail is read, particular cases discussed, and the visits shared. The visiting list is divided quite simply into geographical areas. All necessary certificates are carried. In the closer-packed industrial area 7–8 visits are done in the hour, on the estates 6 and about 5–6 in the residential area. We have all developed the necessary speed to cut out frills and get straight to the point. Visiting continues after lunch—occasionally in the summer visits may be finished by lunchtime. Evening surgery begins at 4.30 p.m. in the residential area, and at 5.30 p.m. in the industrial area, the two sessions dove-tailing. I am home again between 7.30 p.m. and 8.30 p.m.

*Volume of Work*

Last year, 1957, I did 4,550 visits and saw 8,160 patients in the surgery, i.e. a total of 12,710 items. This is approximately 39,000 visits and attendances between us giving a figure of 4·6 items per patient per year. This excludes all hospital visits, telephone calls, &c. Our attendance/visit ratio is therefore about 1·8 to 1, which suggests a high proportion of visiting. The firm conducted 142 confinements last year—a gradual rise from 9 confinements in 1948 to the present figure. Regarding minor procedure—we cope with E.S.R. estimations, hæmoglobins, incision of abscesses and whitlows. Time-occupying procedures, such as removal of sebaceous cysts, are referred to the out-patient department.

We have no outside appointments other than insurance work, and very few private patients. I cover approximately 10,000 miles per year, excluding all private motoring. Night calls vary considerably—on the average each partner will do 20 per year.

In 1952 there were two of us; we shared 7,800 patients; our attendance/visit ratio was 1·3 to 1 and each partner averaged 70 services per day. Then came the Danckwerts Award and we took a new partner in. In six years our list has increased by 600, and we each average 45–50 services per day. So our actual volume of work has greatly decreased, yet the time taken is nearly the same—surely a good thing for both doctor and patient. We are now able to attend post-graduate courses and take part in research recording for the College of General Practitioners.

*Morbidity*

Respiratory disease has by far the highest morbidity rate. Dyspepsia is very common; we have 165 cases of proved peptic ulcer, and 40 odd cases of probable ulcer dyspepsia—an attack rate of about 20/1,000. Rheumatism and the rheumatoid group, hypertension and arterial disease, the neuroses, accidents, sepsis (especially common among the fish workers) seem to provide the most common problems. Illnesses in children, I estimate, occupy one-third of all cases.

**Dr. W. F. Hudson** (Banbury, Oxon):

*Semi-rural*

I propose to discuss briefly some of the facts as I know them about three semi-rural practices. One of the practices, with six partners, has some 20,000 patients on its list; the second, also with six partners, has under 10,000 patients; and the third, with seven partners, has over 12,000 Executive Council patients and retains a number of private patients. Each practice is based on central surgery premises.

The third, the one I know best, occupies the whole of the ground floor of a Victorian house which was built for a doctor in 1877, in the pseudo-Gothic style beloved by John Betjeman but hardly anyone else! Part of it was recently reconstructed at a total cost of about £3,000. An interest-free loan was offered by the Loans Committee but was not accepted by the partners as the Committee laid down certain conditions with which the partners did not agree. One of the stipulations was that there was to be a Partnership Agreement and none of the partners wished for this. It was held, and rightly held as I think, that the interests of a retiring partner or of a widow would be adequately safeguarded by the remaining partners, and would not necessarily be safeguarded by a Partnership Agreement. In this connexion, it is of interest to note the experience of the second six-man partnership which I have mentioned. There, the most junior partner recently admitted was taken with a recoverable but prolonged illness. The other partners looked up the Agreement, which stated that in such a case it was the duty of the sick partner to provide a locum. Knowing the circumstances of the sick man, they of course broke the Agreement and decided to provide the locum out of partnership funds. In my experience, in a happy partnership (and an unhappy partnership should not exist, it is not a partnership at all), the good sense and honour of the partners invariably see that justice is done. Partnership Agreements are like the Law—the accumulation of the wisdom of the past—but, again like the Law, they have not necessarily any great relevance in the circumstances of the present. The accumulated wisdom of seven medical friends, with an outside arbiter if required, is considered

superior to any possible Partnership Agreement. In the practice of which I have experience there were several changes between 1928 and 1948, costing in all in stamped Agreements over £500. In all that time the Agreements were never consulted. When another partner joined us in 1950, therefore, we decided to have no Agreement and we have never had cause to regret that decision.

The partnership employs an adequate staff of competent employees. The secretary occupies a central office adjacent to the reception room at which all messages are taken and appointments made. The secretary's duties include typing all the letters, keeping all the records, supervision of the staff, and dealing with all the day-to-day financial matters. The receptionist makes all the appointments and is in charge of all the record cards. In the evening her place is taken by a part-time receptionist who is invaluable in that she is always available to take over full duties in case of holidays or illness. Two nurses are employed, one full-time and one, a married woman, part-time. The nurse does all the dressings, gives many of the routine injections, does all the sterilizing of syringes and instruments, tests urine, and is available for chaperoning. She occupies a small operating theatre adjacent to two of the consulting rooms and this theatre is used for opening abscesses and other minor operations, besides all the dressings and injections done by nurse. The urines are tested in the old butler's pantry which has been adapted for minor pathological examinations. The health visitors come round one afternoon weekly for discussion about any medico-social problems that may cause anxiety. Their help is quite invaluable in certain difficult cases. The cost of all this ancillary help in salaries and etceteras is about 10% of the gross income of the partnership, but it pays for itself handsomely.

The appointments system is in use. My younger partners have three appointments every twenty minutes; I make one appointment each quarter of an hour and see patients who arrive without an appointment in between. The record cards, in their correct order, are placed in boxes in each consulting room before the surgery, so that there is no last-minute rush to find the card.

As this is a large area covering perhaps 300 square miles, the system of "zoning" has now been started for all patients living outside the town. This has resulted in no great hardship to patients except that they no longer have their choice of doctor. This has been a small price to pay for the advantages that have accrued. It originated when four doctors of the partnership met in a block of Council houses in a village seven miles from the central surgery. Under the new scheme the practice area is divided into three segments of a circle with an approximately equal number of patients in each. Each of the segments is served by two of the doctors, who only go into the other segments in case of emergency. The patients, both State and private, see the point of the arrangement and the advantages to both sides, and there have been few complaints, and none of them serious ones. Mileage travelled has been cut by more than 10%; more time is available for seeing the patients than when each partner was going to all quarters of the practice.

The Regional Hospital Board employs each of the partners at a busy general hospital which has 160 beds. Each partner is regarded by them, either because of higher qualifications or special experience or both, as fit to undertake a specialty. Four are S.H.M.O.s and three are designated "Clinical Assistants" but do full consultant work in the absence of the consultant. They do from two to four sessions a week, and one does eight sessions. As a result, the standard of practice is kept reasonably high and a valued opinion is always available. Incidentally, the Regional Hospital Board is saved the equivalent of at least one, possibly two, consultants.

The practice is blessed with a G.P. Obstetric Unit with 15 beds to which those partners who continue to do midwifery have full access. Few women ask to have their babies at home, though of course domiciliary midwifery is not discouraged.

Each partner is paid 4d. a mile towards his car expenses from partnership funds. This ensures that the younger partners, with fewer hospital and other fixed commitments than the older men, feel that an attempt is being made to equalize car expenses, because their mileage is on the whole greater than the senior men. The partnership owns a car that is always available for any partner whose car is out of action, or it is available for a locum. As a rule, a locum is employed only in August and the first half of September when the partners with school-age children are on holiday.

From the purely management point of view, seven is an unwieldy number of partners. It is sometimes difficult to get them all together at one time, as each has a number of fixed commitments at the hospital or elsewhere. We have not yet managed to get to the position, which holds in the first of the partnerships I have mentioned, where all the partners meet for coffee after the morning surgery, and join in a glass of beer when the evening surgery is over.

The importance of good relations between partners, and between all the doctors in the district, needs no stressing. We feel that we are much blessed in this respect. It is the secret of good partnership management, and everything else is subservient to it.

**Dr. J. D. Huntley** (Nuffield House, Harlow, Essex):

*The Management of a Practice from a Health Centre*

This is an account of a practice from a Health Centre in Harlow—a new town in Essex planned for 80,000 people and where already 45,000 young Londoners live.

Fig. 1A shows the location of doctor, midwife, health visitor and dentist in an established town. All these are involved with the general practitioner's patients. All must express opinions, but as they often work in isolation these opinions may differ and give rise to mutual suspicion. Fig. 1B shows how, in Harlow, all these forces are concentrated in centres such as I shall describe and from the five now established the whole of the medical cover for the area is planned. Nuffield House, where my partners and I practise, is not a health centre within the meaning of the Act, because it was provided by the Nuffield Provincial Trust to whom economic rents are paid. Furthermore, in it a private dental firm is located.

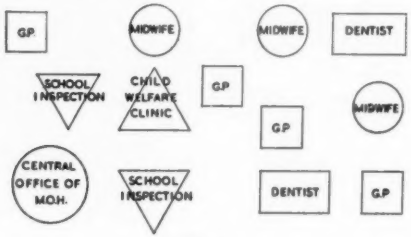



FIG. 1A.

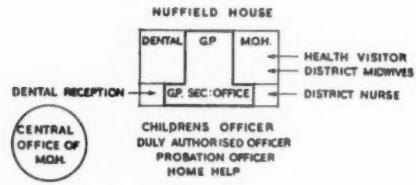



FIG. 1B.

The Trust had in mind small, relatively inexpensive buildings, each to cater for the needs of about 6,000 to 12,000 patients. The aim was to provide a homely atmosphere in which doctors could practise in conditions roughly obtaining in a country town; preserving the identity of the individual practitioner, but integrating with him the ancillary help provided by the Local Authority. In each centre an advisory house committee was set up, composed of representatives of all who work in the building, plus an Executive Council member and one from the Harlow Development Corporation acting for the Nuffield Trust. This committee which at first met every four months, but now only once a year, resolves on the spot any difficulties that may arise.

I hope from such a centre we do provide a good group practice cover for approximately 10,000 people, with four partners, one of whom is a woman. With the county health staff and dental colleagues in the same building it is easily possible for a very close liaison to take place, but it is the individual personalities which will shape the pattern of events and make or mar the spirit of the place. In time differences are resolved and the satisfactory nature of each other's work recognized.

This plan of Nuffield House (Fig. 2) shows, as a main feature, a large central waiting room around which the rest of the building is grouped. This leads to versatility and is an economy for, as the County and practitioners use the same waiting room at different times, the cost can be borne by both. Moveable partitioning is used to divide up the space and provide identity and friendliness for each doctor's waiting group. A good signalling system is also in operation to call in the next patient.

In organizing a practice I believe the secretary's office of the group practice is a most important place and it should be large. It becomes the Common Room at several times of the day. In it one lingers after surgeries and can be found dictating or discussing problems. Notes and hospital reports are at hand and ready answers can usually be given in the secretary's hearing. This is important as she is a vital link in co-ordination and she should be whole-time. She should be a person of some substance with a desire to see that the patient gets a fair deal.

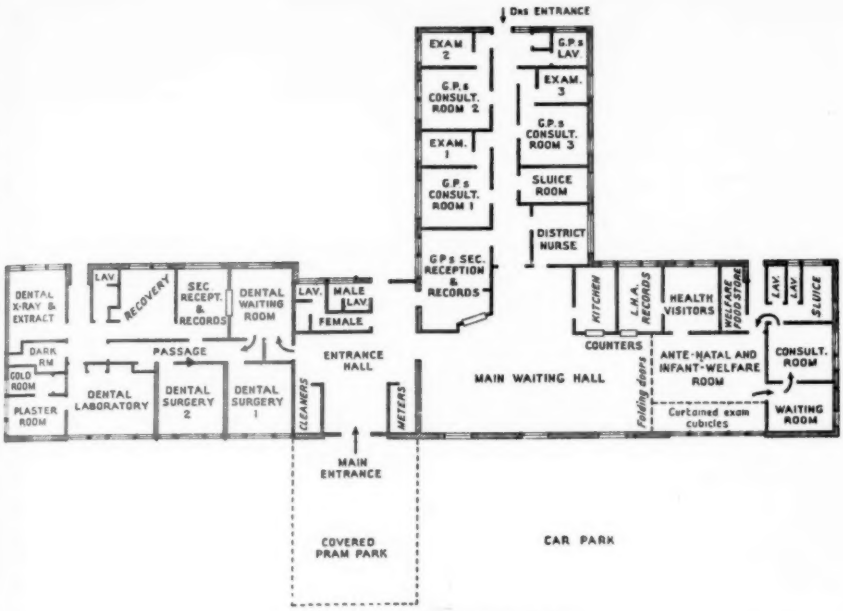



FIG. 2.—The Nuffield Medical Centre.

Nursing attention is given to those patients who can come to the Centre by the district nurse for an hour during the morning surgery in a room provided for her by the County. In the evening, a nurse-receptionist is employed by us.

As practitioners, we are on excellent terms with the Medical Officers of Health, but what is even more important, the district nurse, health visitors and midwives in the Centre appear to like considering themselves as part of a field unit with the practitioners. On clinic days tea is made in our office for everybody including the health visitors and midwives. These observations may appear mundane, but they are the essence of good relations without which I think there can be no advantage in health centre practice.

One of our group conducts two infant welfare clinics a week for the County and is paid by them. It is usually our female colleague and she, with the health visitor, will see sixty or so infants in an afternoon. Thus the practitioners watch the babies they deliver grow up and no cases have to be referred to us from a county medical officer.

Of all the county staff, it is perhaps with the health visitor we work most closely. This is because of the enormous number of babies in the town—371 were born into the practice last year. The mothers are young and there are not many older relatives. It is therefore the health visitor who deputizes for Granny; advising on weaning, clothing and minor upsets in infancy. Test feeds are easily organized, failures to thrive come to notice early, spastics are picked up and large numbers of infants are coped with in a way no single member could do on his or her own. To-day the practitioner is a field worker, leading a team of well-qualified people.

With the passing of the National Health Act the midwife has found herself less of an isolated specialist, but her status must not be reduced to that of a maternity nurse. We have found that mothers who are instructed by health visitors in relaxing classes, who meet the same health visitor, midwife and their own general practitioner in the clinic, are confident and happy. Less and less do they ask if the doctor will be present at their confinement. Because good antenatal care is the key to safe midwifery, I feel it should be the doctor's chief concern and he should, while holding a close watching brief over the whole of the maternity service, personally conduct the antenatal examinations. At delivery, the midwife takes over and he may act almost as a runner, not selfishly stealing anyone's thunder.

Our routine is to make an initial surgery appointment with the mother, so that time can be spent on a full examination and her booking. Plans for her confinement are discussed as well as any fears she may have.

All four of us run antenatal clinics for our own patients in the Local Authority ..ing, with the help of health visitors and midwives. In this way the Local Authority's obli..ation to provide such clinics is met. Here the mother is seen monthly to the thirty-second ..eek, fortnightly to the thirty-sixth and then weekly to term.

Harlow had, incidentally, the highest birth rate and the lowest infant mortality rate in the country, last year.

Having dental colleagues in the same building is a very real advantage; it is usual when the doctor and dentist drain the same area for the patient to belong to each. The patient scores when his professional advisors can consult easily and we will then be found talking together about the rheumatic heart and his penicillin umbrella, about the mouth-breather and his adenoids, about the gastric case and his need for dentures. Team work has developed to a high degree in gas sessions and the availability to the dentist of a doctor for odd emergency gases is welcomed by him.

Rota systems are worked as in any group practice, but the patients are not pooled. Calls handed in before 10 a.m. and patients attending surgery will almost always see their own doctor. One of us will daily take late calls and do week-end and nightly duty in rotation.

None of us specializes in any one particular branch of medicine, but all of us have extra commitments outside the general practice—one covering the Infant Welfare clinics, as I have described, another being responsible for dental gas sessions, while two of us are part-time medical officers in the Harlow Industrial Health Service.

**Dr. P. M. Higgins** (Rugeley, Staffs):

*Appointments Systems*

Our practice consists of six partners, who look after about 15,500 patients; 1,800 of these are in a separate community, one partner being solely responsible for them and he has his own surgery premises. The remaining 13,500, or so, patients are served by a central surgery, and it is here that we have been running an appointments system for nearly three years.

Before going on to consider the lessons of our experience, however, I shall first consider some of the objections commonly advanced against such systems.

The first objection is that the doctor should be prepared to see any patient who attends at his surgery, in case that patient's need is urgent, or in case he may think it is, and this no matter how many may so present themselves.

But, as general practice is at present conducted some restriction is always imposed on the doctor's availability and the patient's ready access to him—the surgery door is closed at a set time and the doctor may do no evening surgery on one or two days in the week. The patient whose illness is so timed that he arrives one minute after the surgery door closes is in no better situation than he who misses the last appointment, and, of course, in any properly run system, whether it embodies appointments or not, provision is made for unexpected and urgent cases. Secondly, it is said, such a system can only be made to work if the practice draws its patients from the higher social groups. Taylor (1954) describes a successful system working in a practice of 2,000 patients in an industrial area. In our own area, where the chief industry is coal mining, 88% of the occupied or retired males aged 15 and over, are in social classes 3, 4 and 5; 34% are in social classes 4 and 5.

The third objection is that patients do not like the system; this has not been our experience; complaints have been few and most arise out of breakdowns in organization for one reason or another.

Fourthly, the patient who decided to come "on the spur of the moment" might be put off if he had to make an appointment. This might be true, but equally uncertain is the deterrent effect on such a person of a crowded waiting room.

Two further objections require closer examination:

An appointments system can never work satisfactorily in general practice because of the great variation in the time needed for individual patients. This is indeed a difficulty and it is increased by the terms under which general practice is done at present—large numbers to be seen, with a wide range of conditions from the most trivial to the most serious. In fact, I would say that, as the problem is presented to us, an approximation is all that is possible—but a sufficiently good approximation to make an appointments system thoroughly worth while.

An analysis of 7 consecutive surgery sessions for one doctor in December 1957 showed that, out of 113 patients, 68 (60%) needed five minutes or less and only 7 (6%) needed fifteen minutes or more.

There are two different ways of using surgery-time; some use it just to sort out their cases, and see patients who need a longer assessment by special appointment or at home; others feel it is best to deal at once with every patient and every problem that comes up. The

doctor who runs an appointment system will need to be flexible in his use of both methods; he will deal at once with what has to be disposed of, but he cannot avoid responsibility for seeing that delays are kept to the minimum. If delays are a regular feature, then the system needs to be adjusted.

Implicit in the last objection to be considered—that such a system will not work because general practitioners' patients need to be seen without delay and cannot wait even twenty-four hours—is yet a seventh fallacy—that an appointments system necessarily means a delay before patients can be seen. We might perhaps dispose of this point at once by considering the actual course of events in our own practice. Our approach was quite simple: as there were three consulting rooms, opening off a long corridor, the flow of patients out of the waiting room and into the consulting rooms had to be organized and this was done by noting the patient's name on a list when he arrived and calling it out when his turn came. When we started an appointments system, it was laid down that every patient, no matter how or when he informed our staff that he wanted to be seen, whether it was before or during a surgery, or whether it was by 'phone or in person, hours or days beforehand, was to be told the time at which he could expect to be seen. It was, in fact, merely a convenient way of forming a queue—but the queue consisted of names in a book and not bodies in a waiting room. We adapted the method described by Dr. de la Tour Mallet (1955) of booking 3 patients every fifteen minutes and found that it worked very well; patients known to require extra time or special examination were allotted a longer period and we saw antenatal patients at separate sessions, but, on the whole, the average of 12 patients booked each hour was found to be about right.

Later on, we went a step farther and used the system to even out surgeries as between different doctors and as between different sessions for the same doctor, in order that, so far as it was possible, no one doctor became over-burdened. The staff were told, however, that the patient alone was to decide: if he wished to see a particular doctor, during a particular session, he was to be allowed to do so; he could be guided but no compulsion was to be used, and if he stated that his need was urgent, he was to be seen. In this way a delay that might be dangerous was avoided.

It seemed to us that we had three categories of cases to cater for in our appointments system:

(1) Non-urgent illnesses, either minor or serious; our impression was that these formed the majority.

(2) Patients with non-urgent and minor complaints who, for reasons of certification, needed to attend on a particular day. Our impression was that this was a large number.

(3) Complaints needing attention that day—injuries, acute infections. Our impression was that these formed a minority.

It was clear that patients in the second category were, however, "urgent" for reasons which arose out of administrative compulsions, determined elsewhere, and not for medical reasons at all. The presence of this group therefore was no argument against an appointments system and all we had to ensure was that patients in the third category received attention when they needed it.

Certain facts suggest that there is normally a sufficient number of non-urgent attendances to make an appointments system worth while: the marked fall in attendances just before public holidays, and at evening surgeries when the weather is bad, and the fact that many patients need to attend more than once. An analysis of two twenty-eight day periods in January and April 1955 showed in fact, that only 40% and 36% respectively of attendances were for the first time; if attendances for one-day illness certificates are subtracted, these percentages are reduced to 33% and 30%.

Of the 113 patients seen in the seven surgeries mentioned above, 38 (33%) attended for the first time; only 23 of these (i.e. 20% of the whole) could be considered "urgent"—in the sense that they would benefit from being seen fairly soon, as opposed to those who would not suffer through delay.

Further confirmation of the fact that the majority of attendances are for non-urgent reasons arises from an examination of appointments actually booked. On three Mondays in October and November 1956, appointments had been booked—by midday the previous Saturday—for 49%, 40% and 55% of the attendances at the morning surgery. For the other days in the four weeks studied, an average of 65% of patients had made their appointments for the morning surgery by the end of the previous day. For the evening surgeries between 74% and 95% of patients were seen by appointment—the figures being counted at least an hour and a half before the surgery began, so as to rule out casual attendances.

A further check was made for the week beginning March 10 this year; this time the number of appointments booked was counted half an hour before the surgery began; in view of the small numbers waiting at the beginning of the surgery, these figures can be considered to

indicate the "organized" stream of patients. Thursday has had to be omitted but at each of the other eight surgery sessions of this week an average of 78 patients were seen (61–95), an average of 7% (4–14%) of appointments were booked but not kept; an average of 78% (62–95%) of appointments were booked and kept.

On Saturday morning 95 patients attended; of these, 87 had appointments booked by 8.30 a.m., at which time there were two patients in the waiting room. At 9 o'clock, when the surgery began, there were 8 patients waiting to be seen by three doctors. In the whole of that week (omitting Thursday) there was an average of 7 patients waiting at 9 a.m. to see 3 doctors and for the whole of the week beginning December 9, 1957 (except Monday, on which no count was made), an average of 3 patients were waiting at 9 a.m. to see 3 doctors. At 9.30 a.m. during these two weeks, there was an average of 7 patients in the waiting room, and over the four weeks for which I have almost complete figures—in October and November 1956, December 1957 and March 1958, the number of patients counted (at half-hourly intervals) in the waiting room never exceeded 21, although up to 125 patients passed through it at one session.

Our results are not always as good as this—delays and hold-ups do occur and, when they do, are almost always the result of a breakdown in organization or to unpunctuality on the part of the doctor rather than the patient. Even when things do not go smoothly, however, there is never the disorganization and gross overcrowding that were invariable features of the old system. The full effects of this change have been described elsewhere (Higgins, 1957); they were quite remarkable. Our waiting room, which, with 60 seats, was far too small to accommodate the numbers who arrived—many of them an hour before the surgery started—is now much smaller, containing only 20 seats, and we have used the space thus freed to good advantage.

This situation may be contrasted with the practice of four partners, described by Taylor (1954), whose waiting room contained 90 seats.

## Conclusions

(1) An appointments system does indeed work in general practice—provided trained ancillary help, covering most of the day, is available. The single-handed or small practice without such help would find it difficult or impossible to run such a system.

(2) It is desirable, because the results achieved are worth the effort involved; patients do not have so long to wait, the waiting-room space can therefore be reduced and the organization of the surgeries is facilitated.

I have tried to think of any possible disadvantages and the only serious one is the occasional happy soul who rings up on his way to work at 6.30 in the morning to make an appointment for that evening.

## References

Higgins, P. M. (1957) *Lancet*, i, 680.
Mallett, A. E. de la T. (1955) *Res. Newsl. Coll. gen. Practit.*, 2, 113.
Taylor, S. (1954) Good General Practice. London.

**Dr. P. A. Walford** (Felsted, Essex):

### *Record Keeping*

The first thing is to decide for whom the records are being kept. Are they for you or are they for some general practitioner of the future who may inherit the patient in after years? If you make notes for yourself they can be much briefer and more compact than if they are made for somebody else.

In my opinion, except in partnerships where the patient is shared, I think it is far better to keep the notes for yourself and to ignore altogether the aftercoming practitioner: all he can possibly be interested in is your diagnosis and your treatment, and if you follow the method that I shall outline he can get those without having to read through your notes. Having decided to be completely selfish about it, your notes should tell you first, the diagnosis if you make one or a key symptom if you do not; the treatment you gave and if it did any good; and of course the main bulk of your notes will be made up of what you want to remember of the patient's symptomatology and your findings.

The golden rules are as follows:

(1) When the patient gets to the end of one illness and starts another, leave a space of two blank lines between the illnesses. This space serves to divide his records up into blocks of writing, each block representing one illness. If you like, draw a line as well.

(2) At some stage you will probably make a diagnosis. Write it in capitals and put a

box round it; if you cannot make a diagnosis then treat the leading symptom in the same way. Your boxed-in word in capitals then acts as the key to the whole of the block of writing in which it occurs.

(3) Keep an inch or so of the right hand side of the record card exclusively for treatment. Do not get your medicines mixed up with the body of the notes where you cannot find them. The average treatment does neither good nor harm, but occasionally you will be gratified by a patient telling you that your treatment has done wonders, and in such cases it is worth drawing an arrow from the treatment in the right hand column to its results in the body of the notes. The same technique of course should be employed if the results of your treatment are particularly direful.

(4) Never write notes on the back of the medical record envelope. This is a wonderful place for recording the patient's past history. Any really important thing that you cannot afford to forget about the patient should be written there, and you put the year of its occurrence in the left hand margin. All sorts of stuff can go in here; things like vegetarian, heavy smoker, alcoholic, widow of a doctor, daughter a trained nurse and so on; and also the various drug sensitivities, and the Rh factor. If a patient's medical record envelope is already covered with writing, the Executive Council will send you a new one if you write to them.

(5) At the bottom of the medical record envelope working from below upwards, write the patient's family history. It is related of one of the older physicians that on ward rounds he did not allow his clerks to read out the patient's family history because it so often gave the diagnosis away. Such considerations need not deter us and if kept reasonably up to date the family history can become an absolute mine of information.

A few other hints:

Staple your records together so that they are not always in a muddle. Staple them down the left hand side and they will then open like a book.

When you get a letter from a consultant make a note of his opinion in the notes; most consultants' letters can be condensed down to one line. The same applies to X-ray and pathological reports. It makes the notes so much more complete in after-years and saves having to ferret through a mass of old letters.

Writing is a slow and clumsy way of putting down your physical findings; it wastes time and however much you write it conveys much less to you than a few lines on a diagram. I have experimented with printed diagrams, and finally adopted this method: diagrams are printed in red on rolls of tear-off adhesive paper. Pain being the commonest symptom of which patients complain, you simply tear off a diagram, stick it on the E.C.7 and shade in the painful area, adding a symbol or two to indicate your findings. With practice you can almost eliminate writing altogether, and the records are far more informative. You will be surprised how much you can learn about pain using this method.

**Dr. Stephen Taylor** (Harlow, Essex):

Management of a general practice is a subject in its own right. In industry, this subject is recognized as such, and much time and research is expended on studying business efficiency and what is now called "work study". In medicine, we are only just starting to realize that the way we do our work can influence both its quality and quantity.

In itself, good management does not necessarily produce good doctoring but it makes good doctoring very much easier. Good practice management is, therefore, not an end in itself, but a means to an end.

Good management can easily be overdone. Over-organization results in what may be termed "garage medicine," where the patients are treated with mechanical efficiency and quite impersonally. This is liable to happen in large partnerships where there is complete pooling of lists and no individual or family interest. Such pooling is not to be confused with the very sensible zoning described by Dr. Hudson.

Under-organization results in fatigue for the doctor, unnecessary irritability and anxiety, the failure to examine properly, and perhaps a higher degree of morbidity for the doctor.

The happy medium relieves the doctor of all that can easily be done by others less skilled than himself, enabling him to concentrate on doing good medicine.

There are three keys to good organization: good practice planning, proper accommodation, and ancillary help.

Dr. Higgins has discussed one aspect of practice planning, namely, the running of an appointments system. This is clearly of great benefit to the patient, but it is also of great benefit to the doctor, inasmuch as it enables him to judge in advance the volume of work facing him at any particular surgery.

Dr. Walford's system of keeping notes and records is admirable. In particular, I would support his plea for the column reserved for treatment and for the diagnosis to be clearly marked after each disease incident.

I would stress the value of the examination-room in a busy general practice. In Nuffield House at Harlow there is a small lobby between each consulting-room and examination-room to act as a sound barrier, so that patients undressing cannot hear the conversation going on in the consulting-room.

With regard to ancillary help, the most valuable single assistant is a skilled secretary-receptionist.

Dr. Huntley is fortunate in that the district nurse is made available to him and his colleagues at their morning surgery, without any additional expense. This is an ideal arrangement and I hope it may be widely extended. The Essex County Council has set an excellent precedent and I trust other health authorities may follow.

Good organisation costs money. The return for expenditure on premises and ancillary help comes in added satisfaction in the work, in knowing that good general practice compares favourably in value to the community and in medical interest with hospital medicine, and in giving the general practitioner time away from his work in which to live his own life, for which, in turn, he is a better doctor.

There are striking variations in the number of acts of service in different practices. In a healthy and prosperous London suburb the figure may be as low as three acts of service per patient per year. The national average is, I think, about 5·5. When I visited Dr. Barnes in the cold, hard, industrial north, he had to give something over eight acts of service per patient at risk, though it is clear that things have improved since then.

In these practices the criteria for consultation are the same for both doctor and patients. There is, in fact, a true difference in morbidity between different areas, as is well shown in the varying infant mortality rates. In one area it may still be over 50 per 1,000 live births; in another as low as 15 per 1,000 live births. Recent arguments in the *British Medical Journal* on this subject are really irrelevant, since both the protagonists were obviously speaking the truth but were practising in areas of very different morbidity.

Eight years ago, general practice appeared to be dying. In these few years a complete revolution has taken place. The scope of general practice is once more rapidly on the increase. There has been a rejuvenation of general practitioner midwifery and an increasing realization on the part of local authorities of the value of having general practitioners to look after their antenatal clinics. The same applies to infant care and the child-welfare clinics. I hope it will not be long before these are everywhere run by general practitioners. The home nurse has always been a linch-pin in the life of the general practitioner. It is a great help to her and to the general practitioner if they can meet daily at the doctor's morning surgery.

More and more experiments in co-operation are showing that the health visitor can be a very positive help in the active practice of social medicine, provided there is regular working contact between her and the general practitioner.

We have heard something, too, of the general practitioner who is a doctor in industry, but that is perhaps another story (Taylor, 1958).

I have taken the importance of group practice almost for granted. It is one of the secrets of good general practice, though there will always be some doctors who are best on their own. The coming of the rotas to our industrial areas has also been a great success.

In this revolution the College of General Practitioners has played a notable part; so also has this Section of the Royal Society of Medicine; so, too, have the many interesting experiments up and down the country in new forms of practice. We have heard something of our experiments at Harlow New Town. The Nuffield Trust has also financed experiments at Darbishire House in Manchester, and at Corby, and there are now a considerable variety of local authority health centres.

The enormous cost of the hospital service represents to some extent the failure of the first line of medical defence, namely general practice. It is both better for the patient and far cheaper for the community if home care under the general practitioner rather than hospital care can achieve equally good results.

## REFERENCES

TAYLOR, S. (1954) Good General Practice. London.

—— (1958) *Practitioner*, **181**, 133.

# Section of Odontology

President—G. T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S., L.R.C.P.

[*November* 25, 1957]

## The Surgical and Prosthetic Importance of the Labial and Buccal Vestibule of the Maxillæ [*Abstract*]

By J. H. LEE, L.D.S. R.C.S., and D. DOWNTON, F.D.S. R.C.S.

*Eastman Dental Hospital, London*

**Mr. J. H. Lee** in his introductory paper discussed problems of retention and stability arising in full denture prosthesis. He showed how various surgical procedures for the correction of abnormalities of the hard and soft tissues of the mouth can be of the greatest assistance to the prosthetist. In the paper which followed, Mr. Downton dealt with the problems raised by Mr. Lee from the surgical standpoint.

**Mr. D. Downton:** Five operations which are used to obtain the requirements of the prosthetists were described. They are in order of sequence: (i) Tuberosity and flabby ridge reduction. (ii) Removal of denture hyperplasia. (iii) Epithelial inlay—by the technique described by Professor H. Björn of Malmö Dental School in his film. These techniques are at present being published in the Proceedings of the British Society for the Study of Prosthetic Dentistry (Downton, 1957). (iv) Frenoplasty—*see* Lee and Downton, 1958. (v) Bone graft to alveolus.

*Bone graft to alveolus.*—In the type of case I shall describe, one finds a very thin and frail ridge, which is markedly undercut. The commonest site is in the incisor and canine region of the maxilla, and not infrequently it appears to have been associated with an old denture carrying the six upper front teeth fitted, or at one time fitted, to the gum. These ridges are usually very tender, even to finger pressure.

To remove these undercuts surgically means the reduction of the alveolar ridge and consequent loss of the sulcus, which we are trying to preserve.

It would seem, therefore, that the correct approach is to preserve what alveolus there is, and at the same time to increase its width by building out the undercut.

Several writers, including Thoma (1952), have described the use of various materials, including tantalum gauze, which can be used for this purpose, but it is generally agreed that autogenous bone is the best. The main contra-indication for its use, however, is the difficulty of obtaining it, and that it is best inserted from an extra-oral approach.

For the past two or three years I have been taking bone from the opposite jaw and inserting it under the periosteum in the undercut region, thus building it out. This has been done by the intra-oral approach. Clinically we have obtained very good results, and patients have been wearing dentures satisfactorily for the past two years on these ridges.

In these cases, there has usually been marked alveolar loss in both maxilla and mandible, and when operating on the maxilla I have removed the posterior portion of the mylohyoid ridge (Downton, 1954) on both sides, together with that portion of attached muscle. This has been minced to a paste, and inserted under the periosteum which has been lifted off the undercut ridge to form a tunnel, by inserting a sharp periosteal elevator through vertical incisions on each side of the undercut (Figs. 1, 2, 3, 4A and B, *see* p. 686[1]).

I learned that the packing out had to be taken to excess. There was a certain amount of resorption after the operation, which continued for about six weeks. Clinically the ridge then appeared to be firm and static and dentures were made.

Earlier this year I wondered if it would be possible to X-ray these grafted areas, and with the help of Mr. Poyton of the X-ray department, Eastman Dental Hospital, we have been able to take X-rays when the graft has been in the incisor region. In the few we have X-rayed, in the maxilla there appears to be a remodelling of the ridge with new bone deposition (Fig. 5A and B, *see* p. 686[1]).

In the mandible when a similar condition presents, I have used bone from the tuberosity region which, of course, has no muscle attached to it, obtaining a clinical result which is equally good, but radiographically the bone chips seem to disappear and are apparently replaced by fibrous tissue. Clinically this technique has been used for the past three years on some 30 patients, and it has produced very good results.

### REFERENCES

DOWNTON, D. (1954) *Dent. Rec.*, **74**, 212; (1957) Proc. Brit. Soc. Study of Prosthetic Dentistry.
LEE, J. H., and DOWNTON, D. (1958) *J. pros. Dent.*, **8**, 19.
THOMA, K. H. (1952) Oral Surgery. 2nd ed. London; Vol. I.

[1]For illustrations to this article please *see* p. 686.

[*January* 27, 1958]

# An Experimental Investigation into the Permeability of Enamel and Dentine with Reference to Its Relation to Dental Caries

By G. C. BLAKE, M.B., B.S., F.D.S.

*Eastman Dental Hospital, London*

PREVIOUS studies, using microradiographic methods (Applebaum, Hollander and Bodecker, 1933; Darling, 1956), have shown that one of the earliest features of dental caries is the appearance in the enamel of areas of demineralization due to the carrying away, in solution, of calcium and other inorganic ions. There is disagreement on the means by which these fugitive ions are brought into solution but it must be accepted that it is the result of the diffusion of demineralizing agents into the lesion and the concomitant diffusing away of calcium, phosphate, and carbonate ions.

In recent years interest has turned towards the small organic part of the enamel. It is thought that destruction or alteration of this organic material may be the principal factor in the complex process of dental caries, but the importance of these organic elements may lie, not only in the provision of a substrate for proteolytic bacteria of caries, but also in the provision of paths for demineralizing and other agents to diffuse into the enamel and ultimately into the dentine, where important changes may be initiated. It must also be remembered that these pathways, though they may be used in disease processes, are normal structures and may well prove to have physiological functions that are not yet understood.

Diffusion in biological systems is seldom free of the control imposed by semi-permeable membranes, and it has been shown in the past that osmotic pressure can be developed *in vitro* across the intact enamel by various solutes (Atkinson, 1947), and it follows, therefore, that *in vivo* water may pass from the pulp and dentine to the mouth or from the mouth to the dentine and pulp in response to the osmotic pressures exerted on either side of the enamel by the saliva and by fluids present in the dentinal tubules. However, at present, we can only guess at the manner in which the osmotic pressure effect functions *in vivo*.

Besides considering the manner of diffusion in the dental tissues it is also important to consider how changes in the structure of the tooth may oppose the passage of solutions by the closure of physiological channels before the onset of caries or by the active production of barriers to the diffusion of harmful substances after caries has begun. Indeed, the establishment of barriers to the diffusion of harmful substances is apparently the most important defence reaction in dental hard tissue.

The permeability of the teeth has often been the subject of research, and in the past many workers have studied aspects of the subject which we have been examining. A review of the methods previously used for the investigation of permeability *in vivo* and *in vitro* and a discussion of the results that were obtained, together with an extensive reference list, is given by Jansen and Visser (1950). In this investigation newer methods of research have been used, where applicable, together with well-known methods, and our results conform with much of the past work.

This work is an investigation *in vitro* on undecalcified material. It falls into three parts—firstly, experiments to trace the diffusion channels in enamel and dentine in sound young teeth; secondly, experiments using the osmotic pressure effect, to measure the rate of water passage across the crown and root in sound teeth; and, thirdly, investigation of the changes in permeability that take place in the dentine as a result of age and caries.

## MATERIALS AND METHODS

Diffusion paths have been examined by tracing the diffusion of 5% mercuric chloride solution, both from the enamel surface and from the pulp chamber. A 5% mercuric chloride solution has a pH of 3·2 which shifts to approximately pH 5 when in contact with the tooth. Most of our experiments have been performed with unbuffered mercuric chloride solutions but more recent experiments, using 2·5% mercuric chloride in 1·0% sodium chloride and borate buffer at pH 7, have yielded the same histological results as those obtained with unbuffered mercuric chloride.

Various metallic impregnations have been used for a long time as "stains" and "markers" to demonstrate histological details and microscopic channels. Salts of silver, gold and other metals have figured in these processes. Lead acetate precipitated by hydrogen sulphide was used by MacGregor (1935) to demonstrate lymphatic channels and dentinal tubules were also demonstrated by this method. Mercuric chloride afterwards precipitated as sulphide was used in 1926 by Nishimura to demonstrate changes in permeability of enamel in caries.

In this work mercuric chloride was chosen as a marker because it is not precipitated by tissue fluid, although it may be readily and permanently fixed in the tooth by precipitation with ammonium sulphide as dense black mercuric sulphide which can then be examined microscopically and its position determined with accuracy. A further advantage is the insolubility of mercuric sulphide in mineral acids so that decalcified sections can be prepared.

The teeth used in these experiments have been fixed in 5% formol saline but other experiments with fresh teeth have shown the same results. The sound teeth were all extracted for orthodontic reasons from children between 11 and 13 years of age.

Undecalcified sections were cut with vulcanite-bonded aluminium oxide discs 3 in. in

diameter and 7-thousandths of an inch in thickness, under continuous water spray. Microradiographs of undecalcified sections 15 to 50 microns in thickness were taken at 5 kV with the Philips Contact Microradiographic Unit.

## Results

The simplest method for tracing diffusion paths is to immerse the tooth in the tracing solution, thus allowing diffusion to take place throughout the tooth, both from the pulp chamber and from the crown and root surfaces. Fig. 1 is a transverse section of the crown of a recently erupted sound tooth which was exposed in this way to a solution of mercuric chloride for twelve weeks. The mercuric chloride was then completely precipitated by immersion of the whole tooth in ammonium sulphide for four weeks.

There is a uniform band of penetration at the surface of the enamel, and the lamellæ and tufts are completely impregnated. If the edge of the peripheral band of penetration in the enamel is examined at a higher magnification, the stain is seen to lie in the region of the prism sheaths.

In young teeth fully impregnated by this method, the mercuric chloride penetration takes place evenly throughout the dentine, completely filling the dentinal tubules and lateral branches (Fig. 2). In these completely impregnated teeth it is sometimes possible to observe dentinal tubules crossing the amelodentinal junction (Fig. 3) and running in the enamel for a considerable distance.

In preparations in which the tooth is impregnated from both the enamel surface and the pulp space, the actual paths taken by the diffusing mercuric chloride from a particular surface cannot be demonstrated. Therefore, a number of teeth were perfused with 5% mercuric chloride, at a pressure of 4 cm. of water, from the outer surface while the pulp chamber was continuously irrigated with tap water by a canula to prevent a backflow of mercuric chloride from the pulp chamber into the dentine. The teeth were sectioned without decalcification under water spray and were placed in ammonium sulphide solution to precipitate the mercuric ion as mercuric sulphide.

Figs 4 and 5 show a section prepared in this way. It was exposed to mercuric chloride for seven days. The sharply defined penetration streams opposite the lamellæ are very striking. There is no penetration of the tufts, which are sealed from the surface by relatively impermeable enamel.

It may be seen that the tufts are normally isolated from the enamel surface, but in some teeth in which the enamel is exceptionally permeable, and in caries, the tufts may take up solution entering from the surface, via the prism sheath paths (Fig. 6). Here the tufts have taken up the mercuric chloride from the surface of the tooth and conducted it to areas in the dentine around the bases of the tufts. This concentration in these regions is thought to be due to ease of access of these areas to fluids entering the dentine from tufts in the enamel. Fig. 7, which is an unstained, undecalcified section cut tangentially to the dentine surface, shows the bases of the tufts at the amelodentinal junction. It can be seen that tufts, like lamellæ, are continuous structures running in enamel in the long axis of the tooth and in close association with the dentine. They may, therefore, represent peripheral longitudinal drainage channels as well as connecting links in the diffusion path between enamel and dentine.

The paths which have been demonstrated are anatomical channels available for the passage of solutions either by flow or diffusion. In the past it has been suggested that there is some circulation of tissue fluid or "dental lymph" through some of these channels (Fish, 1930; Bodecker and Applebaum, 1931). Some of the ideas of "lymph" circulation were based on an incorrect histological concept of the dentinal tubule system due to the misleading appearance of the dental tubules in decalcified preparations, but some form of fluid circulation perhaps within the dentinal fibril may take place. If there is any circulation there are two means by which it may be sustained, firstly, by tissue fluid pressure in the pulp causing a flow outwards in the dentinal tubules, secondly, flow induced by osmotic phenomena which may be towards or away from the dental pulp.

The findings of other workers on the osmotic pressure effect in the crown have been confirmed and it has also been found that the root shows this effect. Advantage has also been taken of the osmotic pressure phenomenon to measure the rate at which fluid passes through the intact tooth as a result of the osmotic pressure developed by 5% sodium chloride solution.

The experimental tooth is attached to the end of a horizontal tube and is surrounded by water contained in an enclosing vessel, while the horizontal tube and the pulp chamber of the tooth are filled with the test solution. Passage of fluid through the tooth can be read by measuring the movement of a marker in the horizontal tube.

The osmotic pressure that develops with 5% sodium chloride is probably many times greater than any pressure which might develop physiologically. The experiment, however, demonstrates the phenomenon and shows the relative permeability to water of crown and root.

The graphs in Fig. 8 show the rates of water passing through premolars of children

aged 12 years. The results vary in different teeth between moderate limits and these are representative results. The shaded part of the graph represents a control period when only water was contained in the apparatus. After ten days the water in contact with the pulp surface of the tooth was replaced by 5% sodium chloride. The rate for the crown is 0·5 c.mm. per day, and for root and crown together is 9 c.mm. per day. By making an estimate of the surface areas involved in each case it appears that for equal areas the root is, approximately, ten times more permeable than the crown.

Permeability in sound young teeth only has been described; now changes developing in older and carious teeth will be considered. For many years since they were first commented upon by John Tomes in 1848 many workers have been intrigued by the translucent regions which appear in teeth, particularly in relation to caries. Such macroscopic translucent regions became the centre of controversy about twenty-five years ago, some considering their appearance to be due to fat or air in the tubules, others attributing the appearance to necrosis of the dentinal fibril. Beust (1931, 1932 and 1934) discusses these views and asserts that the translucent regions are caused by the closure of the dentinal tubules by calcification and that these regions are impermeable to dyes. Fish has contributed greatly to the scientific knowledge of these changes, and in his work with monkeys and dogs *in vivo* described tubules beneath experimental cavities which were blocked by hyaline material which he described as calcific (Fish, 1932). That tubules in a carious tooth can become occluded with mineral salts of high X-ray absorption was shown by Bergman and Engfeldt (1955). As no incontrovertible conclusions appeared to have been reached on this subject and in the light of more recent findings on the normal histology of the dentine (Bradford, 1951; Miller, 1954; Blake, 1958), we examined the translucent tracts which develop laterally to caries of dentine, the translucent tracts in the dentine of the crown in relation to lamellæ, and the well-known translucent regions which appear gradually in the roots of teeth over a period of years.

To demonstrate the complete impermeability of translucent roots such a root was left for a prolonged period in 5% mercuric chloride. Fig. 9 shows an undecalcified section of a translucent root prepared from a tooth which had been immersed in mercuric chloride for six months, after which it was placed in ammonium sulphide until precipitation was complete. A circumscribed area of complete impermeability in the dentine is demonstrated and this corresponds with the area of translucency.

Sections were prepared from the roots of teeth showing these impermeable translucent areas and stained with Schmorl's picrothionin to show tubules. Fig. 10 shows an area from such a preparation where the translucent part of the root dentine adjoins the non-translucent part. The boundary is easily seen between the part of the dentine in which the tubules are occluded and the dentine with patent tubules, although interspersed with the fully occluded tubules there are many which show partial occlusion. This appearance suggests that the highly calcified zone which normally surrounds the tubule is now encroaching on the lumen of the tubule until it is in some cases completely occluded.

A similar area of translucent root was investigated by microradiography. Fig. 11 is a microradiograph from such an area; it shows many of the tubules occluded with a mineral substance of radio-opacity considerably greater than the rest of the dentine matrix. Some of the tubules are completely occluded while others are only partially occluded, again suggesting an abnormal encroachment into the lumen by the normal peritubular calcified sheath. It is considered that the occluding substance consists of a calcium salt, of a composition similar to that of the calcified peritubular sheath.

A similar appearance of translucency can be observed in relation to the lamellæ in the crowns of many teeth after they have been exposed in the mouth for about ten years. These zones appear as streaks in the dentine and follow the track of the dentinal tubules in a similar manner to the tracks of stain entering the dentine from the lamellæ in the sound young teeth (Fig. 4). When these zones are stained by Schmorl's method they are seen to have undergone an occlusion of the tubules similar to that seen in the translucent roots (Fig. 12).

The macroscopic zones and tracts in relation to caries, which were referred to previously, were examined by transmitted light, by the mercuric chloride precipitation method to show permeability, by staining with Schmorl's picrothionin to demonstrate variations in the tubules, and by the contact microradiographic method to show mineralization changes.

The changes of this type which take place in the dentine in relation to caries are variable and inconstant, and we are considering here only one pattern, the development of a translucent zone forming around a tract of tubules which is open to caries peripherally while it is closed at the pulpal extremity by secondary dentine. This tract of open tubules was first observed and described as a "dead tract" by Fish (1928).

When the tooth is exposed to the mercuric chloride at the enamel surface only, the pulp chamber being sealed off, the tract beneath the caries—the "dead tract"—is shown to be permeable as far as the impermeable plug of secondary dentine which closes it off from the pulp (Fig. 13).

If, however, the mercuric chloride is allowed to enter from both the pulp and the crown surfaces (Fig. 14), it can be seen that the dentine is permeable except for a narrow zone on either side of the dentine affected by caries. The dentinal tubules which have become impermeable can be seen to lie beneath sound enamel and are not directly affected by caries. The apparent lateral impermeable zones are a section of a hollow cone of impermeable dentine with its apex towards the pulp. This hollow cone of impermeable tubules corresponds to the zone of translucency around caries.

Thin sections were cut transversely across such a shaft of dentine involved in caries which was surrounded by a ring of translucent dentine. Fig. 15 is a photograph of such a thin transverse section, mounted in water to enhance the appearance of translucency. This section shows the development of several rings of translucency as well as translucent streaks beneath the lamellæ. These sections were examined by microradiography and by staining with Schmorl's picrothionin method.

Fig. 16 shows a microradiograph of half a translucent ring surrounding a shaft of dentine which connected with a carious pit on the occlusal surface. In the enclosing ring nearly all the dentinal tubules are completely occluded with a highly radio-opaque substance. After taking the microradiograph, the same section was stained by Schmorl's method (Fig. 17). Here the correspondence with the microradiograph is well shown. The open tubules are seen to be filled with the Schmorl's "stain", while in the enclosing band of translucent impermeable dentine nearly all the tubules are completely closed.

Examination at a higher magnification (Fig. 18) shows many completely closed tubules, and among them a few fully opened tubules, while others are seen in all degrees towards full closure. The microradiograph shown in Fig. 19 confirms these findings. It was taken from the same area of the same specimen as the previous photomicrograph. At the top, dentine can be seen with the normal radio-opaque peritubular zones. In the middle area of the photomicrograph there is seen the band of calcified tubules, amongst which are many partly occluded tubules, while at the lower margin can be seen dentine affected by early caries. Here, no normal peritubular sheaths are to be seen, but there appears to be no alteration in radio-opacity of the calcified dentine matrix, suggesting that the highly calcified peritubular sheath is the first calcified structure to be lost in dentine caries.

## Discussion and Summary

In young teeth the dentinal tubules which everywhere penetrate the dentine are occupied by the dentinal fibrils. It is not now thought that there is a peripheral space between the fibril and the hard tissue wall of the tubule; however, it is likely that there is free diffusion of soluble substances within the fibril itself though the odontoblast may exercise selection of substances which diffuse into it and thence to the dentinal fibril. When the odontoblasts or dentinal fibrils have degenerated the dentinal tubule becomes a free channel uninfluenced by odontoblast metabolism and is available for the transport of fluid and dissolved substances, either from the pulp or from the mouth via conducting channels in the enamel.

In the enamel there are no pathways comparable with the open tubules of the dentine. However the tufts and the lamellæ provide easy paths for fluid and diffusible substances, and provide passages into and through the enamel. There appear to be no direct communications between these permeable enamel elements and the dentinal tubules. However, many dentinal tubules cross the amelodentinal junction and end in relatively long straight tubes which lie in close association with permeable areas in the enamel.

The dentine matrix at the bases of the lamellæ and at the bases of many of the tufts appears to be permeable. It is chiefly this area which makes possible diffusion and flow from the enamel into the dentinal tubule system and vice versa and may also represent vertical drainage areas in the peripheral dentine. The tufts are normally sealed off from the surface by impermeable enamel. However, in caries and other states of abnormal enamel permeability, the tufts may connect with the surface by abnormally permeable prism sheaths.

Measurements have been made of the rate of flow of water through the crowns and roots of sound young teeth in response to the osmotic pressure effect of 5% sodium chloride. It appears from these measurements that the root is considerably more permeable to water than the crown.

Translucent and impermeable areas that develop in both the crown and root have been shown to be associated with the closure of dentinal tubules with a mineral substance of high radio-opacity. In affected areas all stages of narrowing during closure of the tubules can be found, supporting the view that this is a reaction of individual odontoblast dentinal fibril systems and not a general deposition of calcified material throughout the dentine. It is probably a continuation of the normal peritubular calcified sheath formation. Like the normal peritubular zone, this material occluding the tubules is more radio-opaque than the rest of the intertubular dentine, and on decalcification leaves no organic matrix that can be demonstrated by normal histological methods, so that the tubules which have been occluded are not distinguishable in decalcified preparations.

I wish to acknowledge the help of Dr. C. W. Wilson, of the Department of Physics of the Westminster Hospital, who kindly made available the Philips Contact Microradiographic Unit. I am also indebted to Kodak Ltd. who supplied the fine-grain film for the microradiographs and to the staff of the Pathology Department of the Eastman Dental Hospital, especially Mrs. V. Markies and Mr. A. Smith, A.M.I.L.T., for technical assistance, and also for the advice, assistance and encouragement of Mr. I. R. H. Kramer, head of the Pathology Department of the Eastman Dental Hospital.

## REFERENCES

APPLEBAUM, E., HOLLANDER, F., and BODECKER, C. F. (1933) *Dent. Cosmos*, **75**, 1097.
ATKINSON, H. F. (1947) *Brit. dent. J.*, **83**, 205.
BERGMAN, G., and ENGFELDT, B. (1955) *Acta odont. scand.*, **13**, 1.
BEUST, T. B. (1931) *J. Amer. dent. Ass.*, **18**, 2186.
—— (1932) *Dent. Cosmos*, **74**, 541.
—— (1934) *Dent. Cosmos*, **76**, 305.
BLAKE, G. C. (1958) *Brit. dent. J.*, **104**, 57.
BODECKER, C. F., and APPLEBAUM, E. (1931) *Dent. Cosmos*, **73**, 995.
BRADFORD, E. W. (1951) *Brit. dent. J.*, **90**, 303.
DARLING, A. I. (1956) *Brit. dent. J.*, **101**, 289, 329.
FISH, E. W. (1928) *Proc. R. Soc. Med.*, **22**, 227.
—— (1930) *J. Amer. dent. Ass.*, **17**, 992.
—— (1932) An Experimental Investigation of Enamel, Dentine and the Dental Pulp. London.
JANSEN, M. A., and VISSER, J. (1950) *J. dent. Res.*, **29**, 622.
MACGREGOR, A. (1935) *Proc. R. Soc. Med.*, **29**, 1237.
MILLER, J. (1954) *Brit. dent. J.*, **97**, 7.
NISHIMURA, T. (1926) *Schweiz. Mschr. Zahnheilk.*, **36**, 491.
TOMES, J. (1848) A Course of Lectures on Dental Physiology and Surgery. London.

## LEGENDS TO FIGURES (*see* pp. 683–685).

FIG. 1.—Recently erupted sound premolar. Impregnated with mercuric sulphide. Undecalcified section. ×6.

FIG. 2.—Recently erupted sound premolar showing dentinal tubules cut obliquely. Impregnated with mercuric sulphide. Decalcified section. ×700.

FIG. 3.—Dentinal tubule crossing amelodentinal junction. Impregnated with mercuric sulphide. Undecalcified section. ×275.

FIG. 4.—Recently erupted sound premolar perfused from the enamel surface with 5% mercuric chloride precipitated in ammonium sulphide after sectioning. Undecalcified section. ×7.

FIG. 5.—Area of section shown in Fig. 4 at greater magnification. ×14.

FIG. 6.—Abnormally permeable enamel allowing mercuric chloride solution to enter the tufts and showing concentration of mercuric sulphide precipitate at the bases of the tufts. Undecalcified section. ×15.

FIG. 7.—Unstained section showing the bases of the tufts at the amelodentinal junction. Undecalcified section. ×100.

FIG. 8.—Graph showing rate of water passing through crown and root (curve A) and crown only (curve B). The shaded part represents a control period when water only was contained in the apparatus.

FIG. 9.—Section of a translucent root exposed to mercuric chloride for six months to show impermeability of the translucent dentine. Undecalcified section. ×8.

FIG. 10.—Translucent root showing patent, occluded and partially occluded tubules. Stained by Schmorl's method. Undecalcified section. ×700.

FIG. 11.—Microradiograph of translucent root showing patent, occluded and partially occluded tubules. Undecalcified section. ×600.

FIG. 12.—Translucent streak associated with a lamella showing partial and complete occlusion of dentinal tubules. Stained by Schmorl's method. Undecalcified section. ×450.

FIG. 13.—Preparation to show permeability of "dead tract". Mercuric sulphide impregnation. Undecalcified section. ×7.

FIG. 14.—Preparation to show impermeable lateral zone around "dead tract". Mercuric sulphide impregnation. Undecalcified section. ×8.

FIG. 15.—Transverse section of an adult molar tooth with carious occlusal pits. The section was mounted in water to enhance the appearance of translucency in the rings surrounding shafts of dentine involved in the occlusal caries. Undecalcified section. ×6.

FIG. 16.—Microradiograph of translucent ring around tract of carious dentine. Radiographed at 5 kV. Undecalcified section. ×70.

FIG. 17.—The specimen shown in Fig. 16 stained by Schmorl's method. ×70.

FIG. 18.—Area of Fig. 17 showing partial and complete closure of tubules in the translucent ring. Stained by Schmorl's method. Undecalcified section. ×375.

FIG. 19.—Microradiograph of same area as Fig. 18, showing complete and partial closure of tubules in the translucent ring with a radio-opaque substance. Radiographed at 5 kV. ×375.

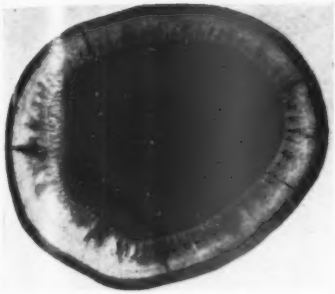


FIG. 1.



FIG. 2.

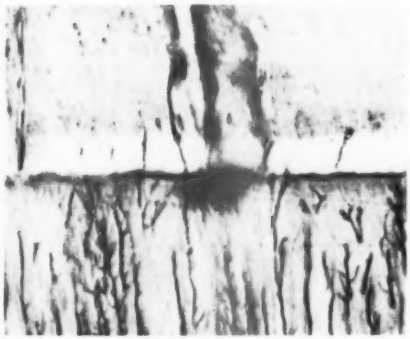


FIG. 3.

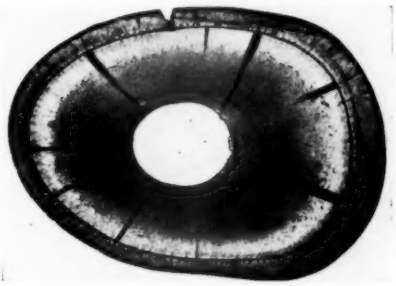


FIG. 4.

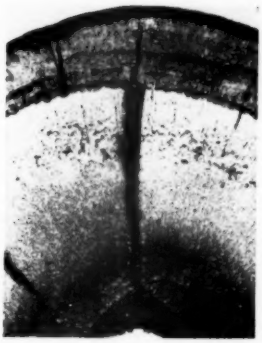


FIG. 5.

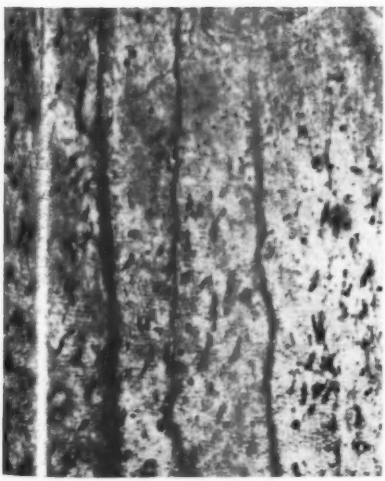


FIG. 7.

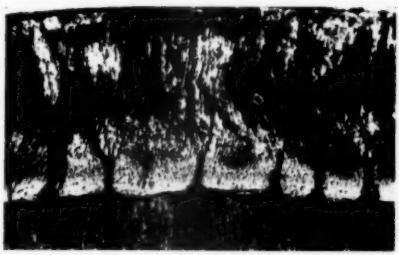


FIG. 6.

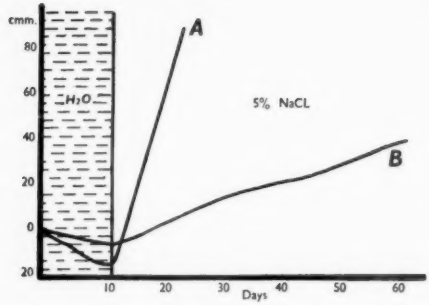



FIG. 8.



FIG. 9.

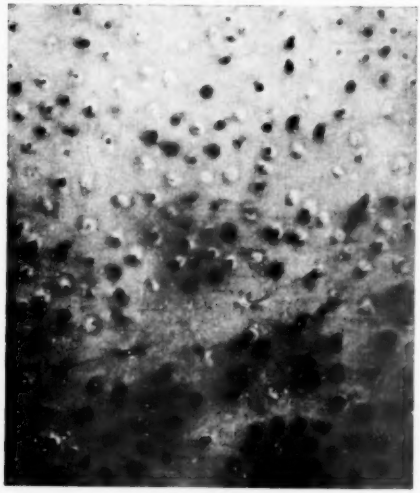


FIG. 10.

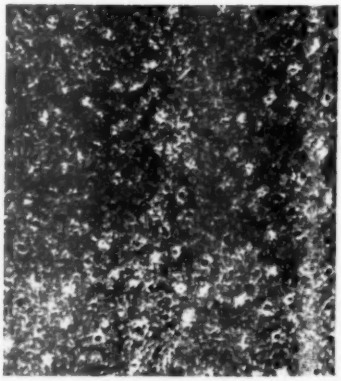


FIG. 11.



FIG. 12.



FIG. 13.

G. C. BLAKE



FIG. 14.

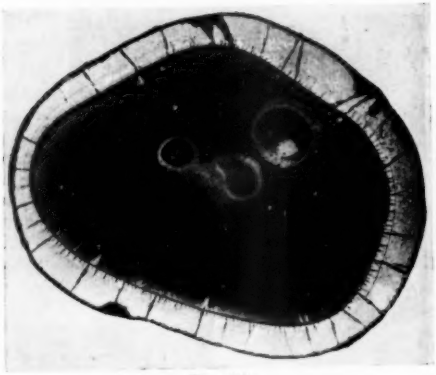


FIG. 15.

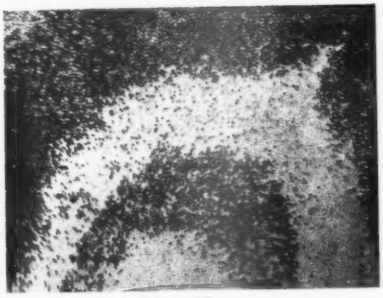


FIG. 17.

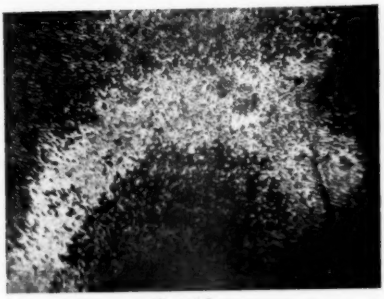


FIG. 16.

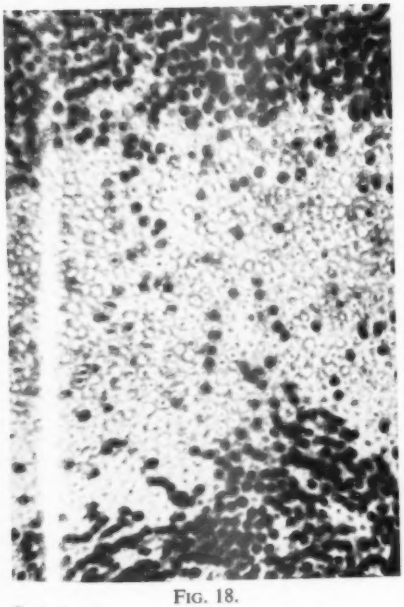


FIG. 18.

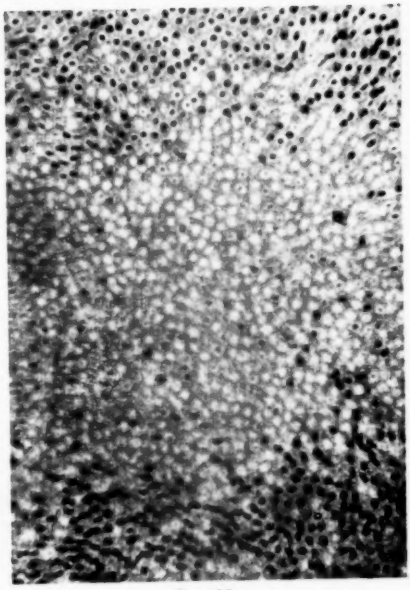


FIG. 19.

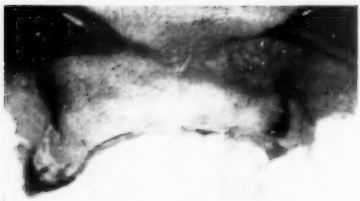


FIG. 1.—Vertical incisions on each side of the undercut ridge.



FIG. 2.—Bone chips being inserted under mucoperiosteum.

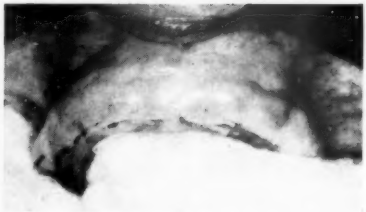


FIG. 3.—Immediate post-operative result with sutures inserted.



A, Before operation



B, Six months after operation

FIG. 4.



A, Before operation



B, Six months after operation

FIG. 5.—Radiograph of same case as Fig. 4.

D. DOWNTON (for text *see* p. 677)



g inserted
eum.

## BOOK REVIEWS

**Drugs. Their Nature, Action and Use.** By Harry Beckman, M.D. (Pp. xvii + 728; illustrated. 105s.) Philadelphia and London: W. B. Saunders Co. 1958.

The author intends this work to serve as a textbook for the undergraduate medical student, to augment the knowledge he gains from lectures and the laboratory. It is written in three main parts. The first is brief and introductory. The second deals with the different ways in which drugs have been discovered and their actions predicted in the treatment of the different maladies to which man is heir; the examples cited illustrate the fortuitous way in which so many remedies, now accepted as specific in the treatment of certain diseases, became known. This section also describes the fate of drugs dispensed in diverse ways, factors influencing their administration and addiction, as well as the question of hypersensitivity. The third section forms the greater part of the book and enumerates the pharmacological action of drugs in the various clinical states.

This is a well-written book and is concise in spite of the wealth of information which it holds. It should be in the hands of every physician. A bibliography is added to each chapter, but in common with many American writers the author accords little credit to workers in the Old World.

**The Life and Work of Thomas Porter McMurray.** By Bryan McFarland. (Pp. 10. 5s.) Liverpool: Liverpool University Press. 1958.

This little booklet embodies the first Memorial Lecture to T. P. McMurray, Professor of Orthopædic Surgery in the University of Liverpool from 1939 to 1947. It is a fitting tribute to one of the big men of orthopædics, written with just the right combination of devotion, insight, and affection. Besides his brilliance as a teacher and surgeon, there are those who will remember particularly McMurray's term of office as President of the British Orthopædic Association and the skill with which he summed up each paper and discussion, making sure that the younger men present retained a balanced view of the subject and appreciated for what they were any questionable opinions expressed. It was a pleasure to read this lecture; no one could have done it better than Bryan McFarland, McMurray's successor in the orthopædic chair at Liverpool.

**Disease in Infancy and Childhood.** By Richard W. B. Ellis, O.B.E., M.A., M.D., F.R.C.P. (Pp. vii + 710; illustrated. 50s.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

Here we have a well-written textbook which not only deals with the disease processes occurring in infancy and childhood, but also integrates the variations that can take place in the growing, healthy child. It is good to know that the clinical approach is used in discussing all problems, for the author was a first-class clinician long before he ever became a Professor. The result is that a clear-cut exposition is placed before the reader, whether the subject matter is organic disease, or behaviour disorders occurring in the growing child.

The work is completely up to date, so that the reader has a clear idea of the different types of drug therapy used.

The true test of the high standard of the book comes in the last chapter on behaviour disorders. In a clear account of these problems the author shows that the pædiatrician must not only be a good clinician, but that he must have a wide knowledge of social and environmental factors, and use his own psychiatric experience so that only a small group of these behaviour disorders need to be referred to the psychiatrist for special investigation and treatment.

**Pædiatrics for the Practitioner.** Supplement 1957. Eds.: Wilfrid Gaisford, M.D., M.Sc., F.R.C.P., and Reginald Lightwood, M.D., F.R.C.P., D.P.H. (Pp. v + 157 + 8; illustrated. 35s. Combined price: £14 10s.) London. Butterworth & Co. (Publishers) Ltd. 1957.

The supplement is divided into two portions, Part I containing original articles, and Part II being the Noter-up whereby the authors give up-to-date information as to the original text of their work.

There is an excellent account of gamma-globulins and immunity, followed by a short chapter on prophylactic immunization, which will be of great value to the practitioner. This chapter has been re-written as great advances in knowledge and methods of immunization have taken place over the past five years. Then follows a chapter on the use of ACTH, cortisone and its derivatives, giving the practitioner an up-to-date knowledge of the true nature of these hormones and indications for their use. A review of congenital heart disease informs the practitioner of the place of modern surgery in relation to the

treatment of these defects. The author gives a good account of the prognosis in relation to the various types of congenital defect, and points out the difficulties arising in diagnosis, and the limitations of surgical treatment in relation to the type of defect. A straightforward account of the diseases and anomalies of the testes and penis is given, and Part I ends with an account of that rare condition of galactosæmia.

This supplement is essential to the volume of "Pædiatrics for the Practitioner". The articles in Part I are original, and the Noter-up keeps the textbook up to date.

**Laboratory Applications in Clinical Pediatrics.** By Irving J. Wolman, M.D. (Pp. xi + 1019. £5 12s. 6d.) London: McGraw-Hill Book Co., Inc. 1957.

Intended for pædiatricians and other practitioners concerned with the medical care of children, this work has been designed primarily to enable the reader to utilize to full advantage the wide variety of laboratory aids. The patient to-day may be subjected to a multiplicity of investigations. Tests, many of them causing discomfort and all of them costing money, may be performed without sufficient thought and discrimination; in the case of children these procedures may easily lead to fear of hospital and the white coat and sometimes to more serious psychological repercussions.

Dr. Wolman has made a detailed survey of the whole field of clinical pædiatrics. Over half of the book's thousand pages are devoted to a consideration of practical aspects of hæmatology, biochemistry and bacteriology. There are chapters about the kidney, the central nervous system, the liver, the gastro-intestinal tract and the endocrine system. Obscure diseases and poisoning are given a brief terminal mention.

Throughout, emphasis is rightly placed as much upon normal physiology as upon the morbid aspects associated with disease. Normal values for infancy and childhood are not neglected amongst the wealth of factual information. The usefulness of the work for diagnosis is enhanced by the provision of a comprehensive cross-referenced index in which presenting symptoms loom large. At the end of each chapter a well-chosen bibliography helps to fill some of the inevitable gaps in the text.

It seems a pity that in a book of this size and from no less an authority than Dr. Wolman, micro-methods, of such fundamental value in the laboratory approach to pædiatrics, have not been considered. In the chapter entitled "Erythroblastosis Fetalis" it is recommended that in certain circumstances serial studies on venous blood to include bilirubin levels "should be repeated every few hours during the first day and at least once daily over the next few days". This advice would be difficult to follow without specialized techniques suitable for specimens of small volume.

The book contains much clinical material, most of it sound, but statements appear here and there which will conflict with the experience of workers on this side of the Atlantic. The chapter "Celiac Syndrome" is particularly notable in this respect.

However, in spite of a few minor imperfections and omissions, this is a reference book of high order which should play an important supplementary role to the other standard texts in pædiatrics.

**Morphine and Allied Drugs.** By A. K. Reynolds, Ph.D., and Lowell O. Randall, Ph.D. (Pp. xiii + 393; illustrated. 80s.) Toronto University Press. London: Oxford University Press. 1957.

Although morphine itself has been known for more than a century and a half, a large amount of work is still being done and is still necessary to unravel the details of its action and the relation of this to its chemical structure. These studies, undertaken partly in an effort to find a non-addicting type of powerful analgesic and partly to disentangle the mechanisms of analgesic action, have already resulted in a considerable deepening of our knowledge and in important additions to the number of useful analgesics now available. The problems of drug distribution in the organism, tolerance, addiction and species variation in response have all been carefully reconsidered in the light of recent knowledge and the subject of the antagonism of morphine actions by nalorphine and levallorphine is well discussed. Here, as elsewhere, the need for further information is obvious. In addition to morphine the other alkaloids of the morphine group are dealt with and also morphine derivatives, together with the phenanthrene group of alkaloids. The second part deals rapidly with the other papaveraceous alkaloids, including those of the so-called Corydalis group. With the exception perhaps of bulbocapnine, these alkaloids have only had the benefit of a preliminary pharmacological study. The third section covers the synthetic analgesics including meperidine, Methadone, alphaprodine and the morphinan series: while the fourth section deals with antagonism to and theories of analgesic activity in relation to chemical structure. This rapid summary gives only approximately the scope of the problems dealt with.

It is an excellent and useful survey of this interesting group of drugs.

**Anesthesia and Otolaryngology.** By Donald F. Proctor, M.D. (Pp. xv + 267; illustrated. 56s.) Baltimore: The Williams and Wilkins Co. London: Baillière, Tindall & Cox. 1957.

This is a fascinating book written by a doctor who has specialized in otolaryngology and anæsthesiology, a very unusual circumstance. It is interesting that the author was an otolaryngologist who has become an anæsthetist, whereas other doctors with dual experience have usually been anæsthetists who became otolaryngologists.

The most striking feature of the book to an otolaryngologist working in London is the difference in professional climate between London and Baltimore. The author pleads for the independence of the anæsthetist and for his status as a medical colleague whose advice and services are sought rather than as an assistant whose help is summoned. This position has already been achieved in London.

The book is very well planned and a sound statement of the general principles of anæsthesia in otoloaryngology and of the management of the respiratory problems associated with otolaryngology. The sequence of chapters and the subdivision of the whole subject is logical and the book can be read as a whole without inducing a sense of irritation because of repetition and contradiction. This is the great advantage of a book written by one author instead of the edited book with contributions by many authors.

However, one cannot help getting the impression that British general anæsthesia has advanced farther than the practice of anæsthesia described in this book. Endotracheal tubes with side openings are thought undesirable in Great Britain yet they are illustrated as standard equipment (page 61). Similarly, the author fears that intubation may damage the voice of a professional voice user (page 60); surely there is nothing to fear provided a sound technique is employed. Tracheotomy is extensively discussed and the reviewer agrees with most of this section, but must take great exception to the statement (page 217) "General anæsthesia is never given for tracheotomy". To a growing body of British opinion, endotracheal intubation to relieve the obstruction should always be a preliminary to tracheotomy, provided the equipment and the skill to use it are available. Once the airway is restored there is no contra-indication to a general anæsthetic.

It would be possible to go through this book and argue about statements made on many pages. Perhaps this is one of the main values of the book to the British reader, as it makes him think about the reasons for continuing his present techniques or perhaps changing to the techniques advocated here.

**Office Gastroenterology.** By Albert F. R. Andresen, M.D. (Pp. xxxiv + 707; illustrated. 98s.) Philadelphia and London: W. B. Saunders & Co. 1958.

Until comparatively recently, we—in contrast with our Continental and transatlantic colleagues—have opposed the acceptance of gastro-enterology as a specialty, regarding it as the province of the general physician. Dr. Andresen's book is a striking vindication of our opinion. An Emeritus Professor of Medicine with a partiality for diseases and disorders of the alimentary tract, his approach has been in the direction of symptomatology. His early chapters deal with general principles, after which he proceeds to individual portions of the alimentary canal and diseases of organs and systems with gastro-intestinal symptoms.

The style is simple, and few typographical errors can be identified; the illustrations, mainly of X-ray photographs, are excellent and admirably support the subject matter. There is perhaps an over-emphasis upon focal infections, condonable as a timely warning, and upon allergy to which rather more exception may be taken.

Clinical medicine does not, on the whole, lend itself to literary elegance but one peculiar feature calls for attention. The author employs the adjective "important" to an extent that suggests a sort of verbal tic. This excellent and valuable treatise, bearing the hallmark of a very experienced clinician, would be improved by re-consideration in the selection of suitable adjectives and in many instances the mention of none at all, when one is, as it were, informed platitudinously that Everest is a very high mountain.

**Biological Aspects of Cancer.** By Julian Huxley, F.R.S. (Pp. 156; 16s.) London: George Allen & Unwin Ltd. 1958.

The author in his preface says "Indeed it may be a good thing to have a few elderly scientists quit of all professional obligations and free to devote themselves now and again to general surveys". It is most fortunate that Dr. Huxley has had the time to make this survey of cancer research. It has been said that already sufficient is known about cancer in order to solve this greatest of medical and biological problems, and it only requires one great brain to co-ordinate all these facts. Dr. Huxley certainly does not subscribe to this view as the book is a mass of suggestions as to further investigations which might

be carried out in order to throw new light on the problem, ranging from experiments on unicellar organisms, botanical studies, melanomata in grey horses (not all malignant) up to the human body. The summary alone under 47 different paragraphs shows an encyclopædic knowledge of the subject. Every research worker in cancer, and indeed in general biology, should read the book, as he will be sure to find something relating to his own particular study.

**A Classified Bibliography of Gerontology and Geriatrics.** By Nathan W. Shock. Supplement One, 1949–1955. (Pp. xxviii + 525. 120s.) Stanford, California: Stanford University Press. London: Oxford University Press. 1958.

A copy of this excellent bibliography should be in every hospital reference library and will be wanted by all those physicians and others who read or write extensively in the subject.

The short and concise introduction written by Shock is simple in style and yet fully adequate as a guide to the supplement. It gives some interesting data and draws attention to the enormous increase in the number of articles contributed to the literature since the publication of the bibliography in 1950. Many of the articles referred to would certainly have escaped the notice of the ordinary busy reader and research worker without the help of this volume.

There is a useful section on "Abbreviations of Journals cited" and a very good index of authors and index of subjects at the end.

The production of this supplement One (1949–1955), as an addition to the bibliography originally published in 1950, has been made possible by The Forest Park Foundation, and they have shown considerable foresight in appreciating the growing interest in the subject which exists to-day and the need for such a bibliography at the present time.

**Fundamentals of Electrocardiography and Vectorcardiography.** By Lawrence E. Lamb, M.D. (Pp. xiii + 142; illustrated. 72s.) Springfield: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

We are discouraged by the author from memorizing electrocardiographic patterns which tell of changes in the heart following disease, and are exhorted to learn from the beginning the laws governing the measurement of potential at the surface of a volume conductor, the fundamentals of vector analysis as a mathematical science, and to distinguish the fundamental difference between polygons and co-ordinate graphs. Is this indeed necessary? What the clinical cardiologist needs is help in the diagnosis of his patient's complaint, and when he turns to the electrocardiogram for this aid, he will gain it by studying the abnormal pattern which it writes. He is not interested primarily in the explanation of the divergence of electromotive forces which has modified the normal design of the tracing. A vectorcardiogram is an extravagant and complex way of depicting the changes written by the electrocardiogram. Naturally, they are bound to be in unison for they are writing the same thing, but the former can never so clearly demonstrate the S–T segment as the latter, and this after all is what interests the physician supremely when the tracing belongs to a patient who complains of pain in his chest. Conventional cardiographic leads, and seven only in number, suffice to tell of ventricular preponderance, either right or left, from defective valve or shunt or as a hypertensive effect, and a ventricular injury from coronary arterial disease, inflammation, toxæmia or electrolytic disturbance, without recourse to a more complicated and obscure method like vectorcardiography.

Chapter 15 on interpretation of the electrocardiogram is well written and gives emphasis to the pervading need of reading the tracing alongside the findings of clinical examination.

**Recent Advances in Oto-laryngology.** By F. Boyes Korkis, M.B., F.R.C.S., D.L.O. 3rd ed. (Pp. viii + 438; illustrated. 60s.) London: J. & A. Churchill Ltd. 1958.

The previous edition of this book was published in 1949 so that the author deals with advances made in the last nine years. Mr. Boyes Korkis has made an excellent choice of subjects without undue emphasis on any of the main sections of oto-laryngology.

This new edition has well-chosen and well-produced illustrations and is a worthy unit of the series begun by Scott Stevenson. The bibliography is reasonably comprehensive and covers adequately the English-speaking journals but, perhaps inevitably, rather neglects publications in other languages. It is only in the publications of the countries where the professions are multilingual, such as Switzerland and Holland, that a good bibliography in several languages can be found.

The author summarizes the views of current writers very fairly and on occasion concludes with his own advice, which is sound. The book is a valuable guide to modern opinions and trends in oto-laryngology and is recommended to specialists and postgraduate students. It is a valuable introduction to the literature of the aspects of oto-laryngology which are under discussion at the present time.

# Section of Odontology

President—G. T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S., L.R.C.P.

[*February* 24, 1958]

## Two Cases of Unilateral Hyperplasia of the Mandibular Condyle

By R. T. BROADWAY, M.D.S., F.D.S., D.Orth. R.C.S.

*Eastman Dental Hospital, London*

THE ætiology of the rather uncommon condition of unilateral hyperplasia of the mandibular condyle is unknown, and various theories have been put forward to explain the excessive growth of the condyloid process. The disorder is in its usual form self-limiting, and varies in duration: there is general agreement that the bone of the excised condyles is of normal histological character, it may show evidence of growth, which in the adult is itself evidence of abnormality; or, if the condition is no longer progressive, there may be no histological abnormality at all. Professor Rushton has reviewed the literature and has found that some of the many ætiological factors put forward in the past can now be discounted, and that the only factors which can still be considered as likely are genetic and traumatic, the latter being difficult to assess since injuries to the jaws are so commonplace, especially in the young. However, if trauma were a factor, there must be a predisposition to condylar hyperplasia, otherwise the condition would be very much more common. Thus, a genetic cause would seem to be the most likely.

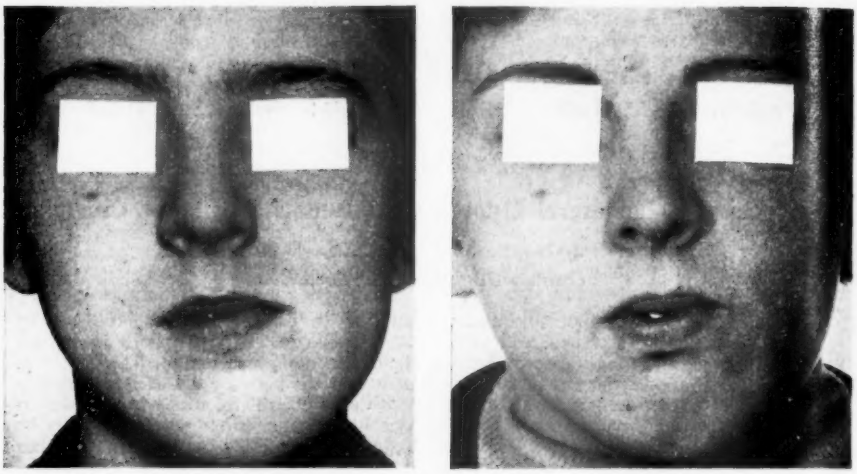
Professor Rushton has shown that whilst the common age for diagnosis of the condition extends from 10 to 24 years, by far the commonest age group is from 15 to 19 years; and that it is probable that the abnormal process started a year or two before the patient or parent sought advice.

The two cases here reported, were referred to the Eastman Dental Hospital for orthodontic opinions, and in both cases facial asymmetry was noted, but was considered to be within the limits of variation from the normal. Careful clinical and X-ray examination over the next few years showed that the asymmetry was increasing and that operative intervention was indicated.



FIG. 1.—Tracings of cephalometric postero-anterior X-rays of Case I, showing the correction of the centre line following condylectomy. Full line: December 1, 1955. Broken line: November 22, 1957.

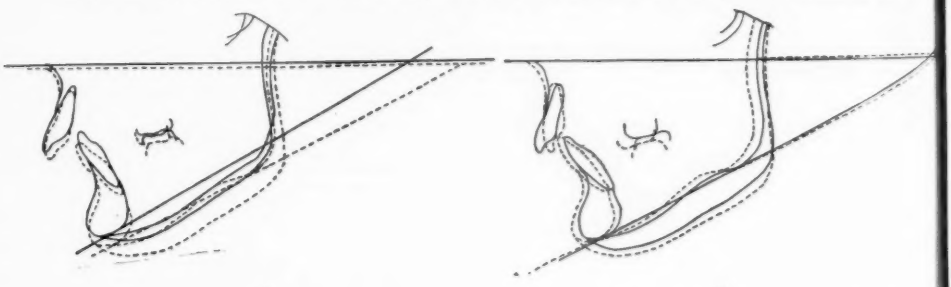
*Case I.*—P. B. This patient was first seen in the Orthodontic Department in 1951, when she was 11 years of age. At that time the following orthodontic diagnosis was made: "Normal skeletal pattern, Angle's Class I malocclusion, with forward shift of all four buccal segments. A mandibular asymmetry was noted, the lower centre being over to the left. The left upper canine was palatally placed." The patient was again referred by her practitioner in December 1955, because he had noted that the asymmetry was more marked. Comparing models taken by the practitioner in March 1955 with those taken in December 1955 it was seen that the lower centre had moved considerably to the left. Further models taken in April 1956, showed that the condition was progressive. The patient was referred to Mr. J. H. Hovell, at St. Thomas's Hospital, for oral surgical advice and treatment. After a period of observation the patient was advised to have her right mandibular condyle excised; this was done in February 1957, the patient being 17 years of age at the time of operation. She made an uneventful recovery, the asymmetry being almost completely eliminated (Figs. 1 and 2A, B).



A B

FIG. 2.—Photographs of Case I showing improvement in asymmetry following operation. A, Pre-operation: December 11, 1956. B, Post-operation: November 22, 1957.

*Case II.*—P. J. This patient was first seen in the Orthodontic Department in 1950, when she was 10 years of age. Her orthodontic diagnosis was: "Skeletal Class II, Angle Class II, Division 1 malocclusion, with a very marked overjet. An enlargement of the right side of the mandible was first noted in 1952, and this was kept under observation. Cephalometric lateral skull radiographs were taken to assess the progress of the condition. A comparison of the tracings of the lateral skull X-rays taken in July 1952 with that taken in May 1954 (Fig. 3A) shows that some general growth of the



A B

FIG. 3.—Tracings of cephalometric lateral skull radiographs of Case II, superimposed on the maxillary plane, showing the increased growth of the right side of the mandible. A, Full line: July 1952. Broken line: May 1954. B, Full line: May 1954. Broken line: August 1955.

mandible has taken place, mainly in a downward direction; but that the difference between the right and left lower borders of the mandible has increased considerably. If we now compare the tracings of lateral skulls taken in May 1954 with that taken in August 1955, we see that there has been a further increase in the growth of the right side of the mandible (Fig. 3B). Orthodontic treatment was being undertaken during this time. Examination of the models taken during this treatment showed that there was little or no change in the centre lines even though there had been considerable growth of the right condyle. There was, however, an opening of the bite in the right premolar region, which may have been due to the increased growth on this side."

The patient was most concerned at the progressive nature of the condition and was referred to Mr. Hovell at St. Thomas's Hospital who, after a period of observation, advised her to have the right condyle removed. This was performed on April 17, 1956, the patient making an uneventful recovery. Pre-and post-operative photographs (Fig. 4A, B) show the improvement in the asymmetry. The pathologist's report on the excised condyle showed, "Actively growing condylar cartilage, endochondral bone formation is progressing normally. No other histological abnormality noted". Models taken eighteen months post-operatively showed no change in the occlusion.



A B

FIG. 4.—Photographs of Case II, showing improvement in asymmetry following operation. A, Pre-operation: March 2, 1956. B, Post-operation: November 6, 1956.

These two cases differ a good deal, the first showing considerable changes in the occlusion, the centre line swinging markedly towards the unaffected side; the second shows no swing of the centre line, but at one stage developed an open bite in the premolar region of the affected side. It may be that in this case the soft tissue activity of the tongue, lips and cheeks, together with the fact that she was having orthodontic treatment at the time, has compensated for any centre line shift.

Neither patient has suffered any post-operative discomfort, and both have a full range of mandibular movements, with only a slight swing to the operated side on opening. Mr. Hovell informs me that he has now excised a number of condyles for this condition and that in no instance has there been any post-operative discomfort in either the operated or unoperated joint. This is in contrast to those cases in which condyles are excised for pain due to a derangement of the temporomandibular joints; in which case it is not uncommon to have the patient return complaining of pain in the previously unaffected joint.

These two cases were diagnosed at an earlier age than the average found by Professor Rushton and it is interesting to note that, although the mandibular asymmetry was observed when the patients were first seen, it was considered to be within the outer limits of normality.

There has been some discussion as to the best age to operate on this type of case. Gruca and Meisels say, "The earliest resection is not only advisable but absolutely indicated". Rushton gives a warning against too early operative procedures, in that too early an operation may make that side of the jaw too short, and secondly, it is essential to make sure that the condition is progressive: he feels that the right course is to wait until a point has been reached when condylectomy will leave both sides approximately equal. This latter is undoubtedly the right course to take.

My thanks are due to Professor C. F. Ballard and Mr. J. H. Hovell for permission to present these two cases which differ so widely in their clinical manifestations; and to Mr E. Morgan and his staff in the Photographic Department, Eastman Dental Hospital.

## REFERENCES

GRUCA, A., and MEISELS, E. (1926) *Ann. Surg.*, **83**, 755.
RUSHTON, M. (1946) *Proc. R. Soc. Med.*, **39**, 431.
—— (1951) *Int. dent. J., Lond.*, **2**, 41.

# Bilateral Ankylosis of the Temporomandibular Joints Following Rheumatoid Arthritis

By H. P. Cook, M.B., B.S., B.D.S., F.D.S. R.C.S.

*Westminster Hospital, London*

The temporomandibular joints are sometimes involved together with the peripheral joints in rheumatoid arthritis. Occasionally they may be the first joints affected in the course of the disease, but in either case ankylosis of the joints is uncommon from this cause. Comroe (1953) was in agreement with this view.

The Empire Rheumatism Council (1950) in a review of 532 patients gave the order of onset of joint involvement. The peripheral joints were first affected in 67% of cases, the proximal joints in 29% and the spine in 4%. The temporomandibular joints were not mentioned.

Thoma (1946) reported a series of 18 cases with ankylosis of the temporomandibular joint, of which 6 were the result of rheumatoid arthritis. The head and neck of the condyle were often enlarged, as well as ankylosed, so that osteo-arthrotomy was required to restore function. This was successfully carried out on six joints in his cases.

A comparable series reported by Kazanjian (1938) consisted of twenty-eight ankylosed joints of which three were the result of rheumatoid arthritis. This author defined complete ankylosis as less than 5 mm. of anterior opening. This small amount of movement was accounted for by elasticity of the mandible or sutural movement. The operation recommended was arthroplasty carried out through the condyle neck, and gave good results in the 3 cases reported.

Still's disease has also been described as a progressive cause of bony ankylosis of the joint. Dingman (1944) reported such a case, successfully treated by osteo-arthrotomy.

## Case History

Male, aged 49, who worked as a gardener. His first symptoms of rheumatoid arthritis appeared in 1928 when he noticed stiffness of the joints of his thumbs and big toes.

Other joints gradually became involved until by 1934 he was so ill as to be completely bedridden on account of pain and swelling affecting most of the joints of his body. His temporomandibular joints were first involved at that time, and the acute pain and swelling lasted for about four weeks. Its disappearance, however, left him unable to move his lower jaw, and he did not think that this had improved or deteriorated in the intervening twenty-three years. He had also suffered from psoriasis arthropathica for seventeen years.



Fig. 1.—Pre-operative ankylosed state.

His chief complaint was difficulty in eating. He could manage only very soft foods, and this very slowly.

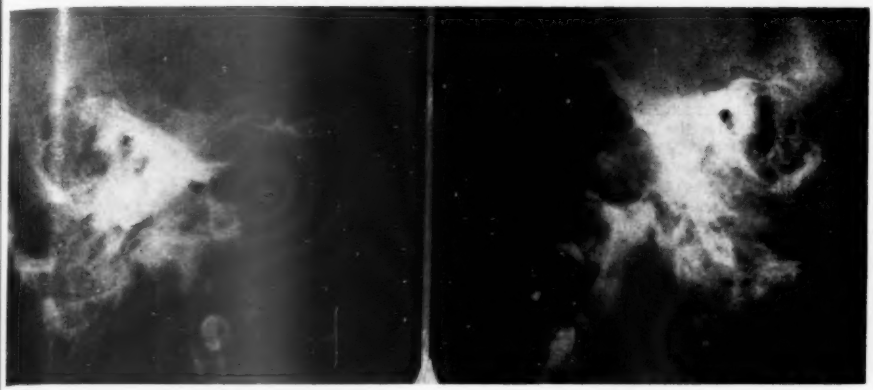
*On examination.*—He was unable to open his mouth. With a great effort he could produce about 2 mm. anterior movement of the lower jaw. The temporal muscles were wasted. His teeth were represented by a collection of carious stumps, although the full complement was present (Fig. 1).

His hands were grossly deformed with the fingers fixed in bizarre positions. The wrist-joints were also ankylosed and there was limitation of movement in the knee, ankle, elbow and shoulder joints. These findings were confirmed by X-ray investigation. Films of the temporomandibular joints showed complete bony ankylosis on the right side and partial bony ankylosis on the left (Fig. 2 L, R).

*Investigations.*—(*Blood:* Hæmoglobin 91%) W.B.C. 8,500 (Polys. 90%), E.S.R. 9 mm. in the first hour (Wintrobe). Liver function tests: Colloidal gold 0 units: mercuric chloride 3 units. Rose's test: Agglutinin titre against sensitized sheep's cells 1/8.

It was decided that this was a burnt-out case of rheumatoid arthritis, and the best chance of getting a functional result would be to perform bilateral osteo-arthrotomy of the joints. This was carried out with difficulty.

On the right side complete bony ankylosis was present with deformity of the condyle. There was bony filling in between the zygomatic arch and the sphenoid, and the temporalis was a wasted slip. The condyle, coronoid process and a segment of zygomatic arch were removed piecemeal using osteotomes. On the left side bony ankylosis across the joint space was incomplete. Again most of the condyle and the whole coronoid process were removed in pieces with osteotomes. On both sides a gap of ¾ in. was created between the condyle stump and the glenoid fossa. Into the spaces prepared flaps of temporalis were sewn. At the end of the operation, an opening of two finger-breadths was present anteriorly between the teeth.



LEFT RIGHT

FIG. 2.—Pre-operative X-rays. Left and right temporomandibular joints showing bony ankylosis.



FIG. 3.—Post-operative X-rays. Left and right temporomandibular joints showing open positions.



A B

FIG. 4A and B.—Showing extent of post-operative movement.

Post-operative course was uneventful, with remarkably little hæmatoma formation. A five-day course of intramuscular penicillin was given. After three or four days, the patient began to gain control over his mandibular movements and was placed on active physiotherapy.

A temporary weakness of the left frontalis muscle was noticed, but this rapidly recovered.

*Histology* of the bony fragments showed some erosion of the remaining articular cartilage with no specific changes of rheumatoid arthritis.

A month after the first operation the remaining roots were removed and immediate dentures were fitted. These have since been rebased. Total admission period was seven weeks.

His mandibular movements have continued to improve since discharge and are now slightly better than initially. These are mostly hinge in type with very little lateral excursion (Figs. 3 L, R, and 4A, B).

I should like to thank Mr. R. Sutton Taylor for permission to report this case. I am also grateful to Dr. Peter Kerley for the X-rays and Dr. Peter Hansell for the photographs.

REFERENCES

COMROE, B. I. (1953) Arthritis. 5th edit. Editor: J. L. Hollander. London.
DINGMAN, R. O. (1944) *J. oral Surg.*, **2**, 71.
EMPIRE RHEUMATISM COUNCIL (1950) *Brit. med. J.*, i, 799.
KAZANJIAN, V. H. (1938) *Surg. Gynæc. Obstet.*, **67**, 333.
THOMA, K. H. (1946) *Amer. J. Orthodont.*, **32**, 259.

## Melanoma of the Hard Palate

By G. S. HOGGINS, B.D.S., F.D.S. R.C.S., and
K. R. THORNTON, B.Sc., M.B.

*Birmingham*

THE pathological diagnosis of malignant melanoma has been facilitated by Allen's description of a large series of proven cases (Allen, 1949), and by his formulation of pathological criteria to aid the diagnosis. Particular emphasis is laid upon an appearance in the lower layers of the epithelium of the affected area, which Allen refers to as "junctional change". This change is almost invariably found in premalignant and malignant melanoma. Together with a malignant cytology and invasion of the dermis, it is essential to a diagnosis of malignant melanoma. These characteristic changes are shown in the following case:

The patient, a man aged 48, first seen in May 1955, complained of irritation in the front of the palate which had increased latterly and had given rise to some swelling which interfered with the wearing of his upper denture. The condition had first been noticed some five or six weeks previously. The patient's general health was good and there was no significant medical history.

*On examination.*—A round purplish vascular area about 2 cm. in diameter was seen in the anterior part of the hard palate left of the mid-line. It was firm in consistency with no surrounding induration, and was only slightly tender to touch. An inflamed area of the mucosa was situated more labially and in the mid-line. One well-defined lymph gland was palpable beneath the angle of the lower jaw on the left side.

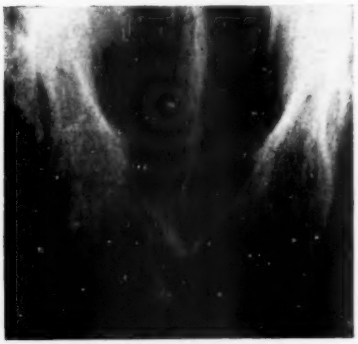


FIG. 1.—Circular radiolucent area in region of anterior palatine foramen.

X-ray examination revealed what appeared to be two distinct lesions. The first was a clearly-defined radiolucent area in the region of the anterior palatine foramen, suggesting the possibility of an anterior palatine cyst (Fig. 1). The second, to the left of the first, was an area of osteoporosis corresponding with the site of the purplish lesion in the palate.

With regard to the clinical diagnosis, the short history coupled with the discomfort and the rapid swelling in the palate, at first suggested an inflammatory condition. The radiographic appearance showing an area of bone rarefaction in immediate relationship to the palatal swelling seemed to support this. The presence of an anterior palatine cyst appeared as a separate lesion. The purplish colour of the lesion and its firm consistency on clinical examination suggested the possibility of a hæmangioma. However, the hard isolated cervical lymph node found to be present raised the question of a more serious lesion.

Surgical exploration was undertaken under nasotracheal anæsthesia. The purplish lesion was radically excised and this gave rise to considerable hæmorrhage. During the removal of the underlying osteoporotic bone, the mid-line cyst was entered, and there was a discharge

of yellowish fluid. The cavity was cleared and the large residual wound was packed. The specimen removed from the hard palate was sent for histological examination. Post-operative healing was uneventful.

*Histology.*—The fragment of tissue was covered by a non-keratinizing squamous epithelium showing pseudo-epitheliomatous hyperplasia and containing a large amount of glycogen, stained in the PAS method and removable by diastase incubation (Fig. 2).

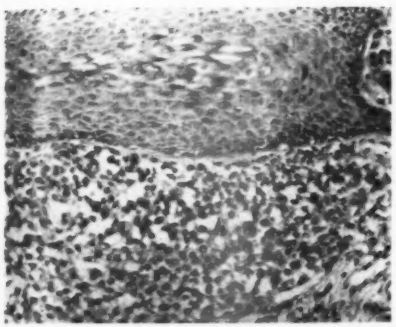


FIG. 2.—Pseudo-epitheliomatous hyperplasia and tumour cells in dermis. ×104.

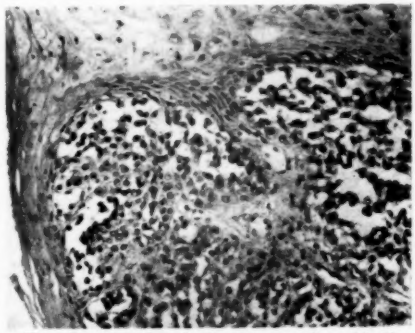


FIG. 3.—Junctional change, pseudo-epitheliomatous hyperplasia, and dermal tumour cells. ×104.

The stratum malpighii and lower stratum spinosum show ballooning of epithelial cells, anisocytosis and hyperchromatism, loss of prickles and enlargement and irregularity of nuclei and nucleoli. This is the epidermal picture of junctional change (Allen, 1949), a constant feature of malignant melanomata.

With silver impregnation of reticulin fibrils and PAS staining, the basement membrane is incomplete in the areas of junctional change. From these areas, groups of cells deeply invade the corium, and smaller groups and individual cells are penetrating the upper layer of the epithelium. Occasional very large anaplastic cells are seen, and mitoses are fairly frequent. Both in epithelium and tumour there are a few cells containing melanin granules. The tumour is a malignant melanoma.

Following the operation in May 1955, there was a gradual increase in the gland mass in the left side of the neck. At that time, after due consultation, it was considered unlikely that treatment by surgery would be of benefit. The use of radiotherapy, which is generally not effective on these tumours, was also ruled out.

The patient remained well, however, for a year and there was no recurrence at the site of the primary lesion, but in July 1956 proptosis of the right eye developed, and was attributed to an intra-orbital secondary deposit of the tumour. In August 1956 this lesion was treated with radiotherapy and receded considerably, but a month later the patient had lost much weight and complained of severe epigastric pain and anorexia. He died in December 1956, i.e. twenty-one months from the onset of symptoms. No necropsy was obtained.

Malignant melanomata of mucous membranes are probably not so rare as is generally supposed, forming 15% of the series described by Allen. Up to 1921, however, only 25 cases of malignant melanoma of the palate had been reported in the world literature, and these were reviewed by New and Hansel (1921). These authors referred to the tumour as "Melano-epithelioma" and clearly indicated the alteration of epithelium, destruction of rete pegs, and pre-existing melanosis as characteristic features.

In a series of 337 malignant melanomata studied by Allen and Spitz (1953), 8 cases (2·3%) involved the palate. The histological criteria of malignancy formulated by Allen for the skin also applied to the palate; these criteria are: pseudo-epitheliomatous hyperplasia and junctional change in the epithelium, malignant cytology, and invasion of epithelium and corium by malignant cells (Fig. 3). The uniformly bad prognosis of the mucosal tumours was noted. There is no evidence that malignant melanoma is more common at embryonic closure lines, and the significance of the association in this case with a mid-line cyst cannot be assessed.

We wish to acknowledge the help received from Professor E. B. Manley and his department of Dental Pathology at the University of Birmingham.

## REFERENCES

ALLEN, A. C. (1949) *Cancer*, **2**, 28.
——, and SPITZ, S. (1953) *Cancer*, **6**, 1.
NEW, G. B., and HANSEL, F. K. (1921) *J. Amer. med. Ass.*, **77**, 19.

# Malignant Melanoma of the Hard and Soft Palate

By W. B. HALES, T.D., F.D.S. R.C.S.

*Stafford*

M. P., female, aged 51, originally observed two small black spots in the centre of her hard palate. She did not seek any medical advice till some four years later when the condition had progressed to that shown in Fig. 1. In November 1956, practically the whole of her hard palate was involved with a considerable extension into the soft palate. No lymphatic spread was detected and X-rays of her lung fields appeared clear. A biopsy from the left side of her hard palate confirmed the diagnosis of malignant melanoma.

I decided to remove the palatal mucosa as widely as possible, extending the operation as far beyond the limits of the pigmentation as practicable and to cover the surface exposed with a Thiersch graft, an appliance being made to maintain this in position. The operation was uneventful, the posterior palatine vessels being divided on each side. The bone underneath appeared normal and the mass shelled easily away from the hard tissues. The extent of the area removed can be seen in Fig. 2. The patient was sent home seventeen days later, islets of the skin graft having taken satisfactorily. The histology in Fig. 3 shows spindle-shaped cells packed with pigment.

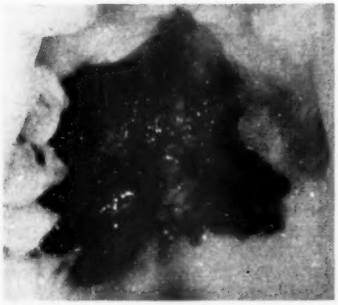


FIG. 1.

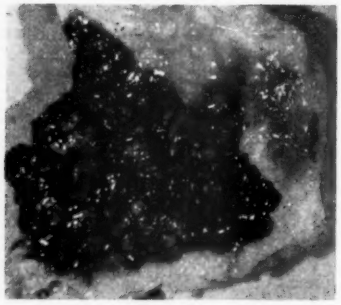


FIG. 2.



FIG. 3. (×1,000).

Three weeks later a lymphatic swelling was observed at the anterior border of the right sterno-mastoid. A block dissection of the glands on this side was advised and an extensive chain of pigmented lymph nodes was removed and the whole area left clear.

Five months later further lymph nodes were palpated behind her right ear and these became more marked during the next two months. By the end of September 1957 she had a paralysis of the right external rectus muscle for which she had to wear an eye shade, pain in her right tibia together with porosity of one rib. On October 13 she relapsed into unconsciousness and died three days later, eleven months since she was first seen. There was never any evidence of a local recurrence.

From the beginning, the possibility of radiotherapy was considered and this was reviewed as the disease progressed but the radiotherapist did not advise any treatment on these lines.

## REFERENCE

CADE, S. (1957) *Brit. med. J.*, i, 119.

# Section of Experimental Medicine and Therapeutics

President—J. V. DACIE, M.D., F.R.C.P.

[*March* 11, 1958]

## Acquired Hæmolytic Anæmia

### PRESIDENT'S ADDRESS

By Professor J. V. DACIE, M.D., F.R.C.P.

*Department of Hæmatology, Postgraduate Medical School of London*

IT is exactly sixty years ago since Hayem in France published a paper entitled "On a particular variety of chronic icterus—chronic splenomegalic infectious icterus"; in this paper anæmia with jaundice was differentiated from disease of the liver. Fifty years ago, in 1908, we find, also in the French literature, the first clear descriptions of acquired hæmolytic anæmia under the title "acquired hæmolytic icterus" (Widal *et al.*, 1908*a*, *b;* 1909). A year later, in 1909, so-called hæmolysinic icterus, associated with hæmoglobinuria, was described by Chauffard and Vincent. Widal and his co-workers stressed that autohæmagglutination was characteristic of the cases they studied and they made a clear distinction between acquired and congenital cases of hæmolytic anæmia on both clinical and laboratory grounds.

The pioneer work of the French physicians preceding the First World War was largely forgotten in the two following decades, and the very existence of acquired cases of hæmolytic anæmia, as opposed to congenital cases, manifesting themselves later in life, doubted. It was not until the papers of Dameshek and Schwartz (1938*a*, *b*; 1940) that acquired hæmolytic anæmia was generally recognised as a separate disease syndrome.

The absolute separation between the congenital and acquired types was confirmed in 1943 when Mollison (Dacie and Mollison, 1943) demonstrated that, whereas in hereditary spherocytosis normal red cells survived for a normal length of time in the patient's circulation after transfusion, in acquired hæmolytic anæmia the normal cells were eliminated far more rapidly—that is to say, they seemed to be destroyed by the same mechanism as was destroying the patient's red cells. A congenital defect of the patient's red cells was thus ruled out.

The next major step in the understanding of the acquired hæmolytic anæmias was the application of the antiglobulin test of Coombs *et al.* (1945) to the investigation of cases of hæmolytic anæmia. The test was soon found to be negative in congenital hæmolytic anæmia, but often positive in the acquired type. The first observations were reported by Boorman *et al.* in 1946.

Since that time it has been generally accepted that the central pathological feature of acquired hæmolytic anæmia is, in most instances at least, the formation of anti-red-cell antibodies which are adsorbed to, and thereby damage, the patient's own red cells. In the minds of most people this brings acquired hæmolytic anæmia into the debatable category of disorders brought about by "auto-immunization", and the term "auto-immune hæmolytic anæmia" is now widely used as a descriptive title. In this paper I shall consider pathogenesis—that is to say, the mechanism by which hæmolysis is brought about, using the term hæmolysis to denote in this context simply an accelerated rate of red-cell destruction.

### *Pathogenesis of Acquired Hæmolytic Anæmia*

There have been two main approaches to this problem. First, experimental work on animals in which hæmolytic anæmia has been brought about either by the administration to an animal of a hæmolytic hetero-immune serum prepared in an animal of another species by repeated injections of the experimental animal's red cells, or by studying incompatibility reactions within a species, for example, by injecting an iso-immune serum. Secondly, observations on man himself, such as what can be learnt by investigating the nature and reactions *in vitro* of the auto-antibodies, by studying the effect of splenectomy, or by seeing how the patient deals with red cells which have been tagged with radioactive chromium.

I have not referred to the experimental production in animals of an acquired "auto-immune" type of hæmolytic anæmia, analogous to the spontaneously-occurring disease in man. To the best of my knowledge no one has yet succeeded in producing such an anæmia experimentally.

### *Experimental Work in Animals Using Hetero-immune Sera*

Belfonti and Carbone in 1898 and Bordet, also in 1898, are usually credited with being the first to study the harmful effect on an animal of injecting it with a hæmolytic immune serum, and it was not long before it was realized that this procedure might result in marked anæmia, often with hæmoglobinæmia and hæmoglobinuria (Cantacuzène, 1900; Kraus and Sternberg, 1902; Levaditi, 1902). Levaditi in 1902 demonstrated that erythrophagocytosis occurred in the spleen and concluded that this was probably an important mechanism, but not the only mechanism, leading to anæmia and hæmoglobinuria. In Britain, experimental work of this sort seems to have been undertaken rather later, but in 1908 Dudgeon *et al.*, described the distension of the spleen with red cells, with evidence of abundant erythrophagocytosi and the development of hæmolymph glands, which followed the administration of hæmolytic sera.

*Work of Muir and McNee.*—The paper of Dudgeon *et al.* was followed in 1911 by the classic description of Muir and McNee: they worked with rabbits given hæmolytic immune sera derived from goats, and they described in detail the consequent blood changes. Their paper contains some good photomicrographs, and although they do not actually use the term "microspherocyte", they certainly illustrate them and comment on their presence. The following is part of what they say: "As the anæmia progresses many of the old erythrocytes seem to diminish in size, so that many corpuscles of 3–5 $\mu$ in diameter, which stain deeply with eosin, are present. At the same time, the larger newly formed corpuscles gradually lose their basophil reaction, and it would appear that some of them undergo contraction and diminution in size." Later on in their paper they note that the microcytes disappeared quickly as the animals recovered and conclude that this is probably the result of their being destroyed.

Muir and McNee go on to discuss the mechanism of anæmia and compare the degree to which overt hæmolysis could be produced by experiments *in vivo*, and *in vitro*, as the result of the interaction between red cells, antibody and complement. They made the point that the amount of blood destruction produced *in vivo* by a particular dose of immune serum was always far greater than that which would be expected on the basis of experiments *in vitro* and they reached the important conclusion that the course of events in the experimental animal could not be explained by the principles which governed the development of hæmolysis in the laboratory.

*Banti's contribution.*—Banti (1913) carried out similar experiments to those of Muir and McNee, but used dogs as well as rabbits, and although he did not study red-cell morphology closely, he measured osmotic fragility and also considered the role of the spleen in hæmolysis. Like Muir and McNee, he was struck by the much greater activity *in vivo* of hæmolytic immune sera compared with their ability to cause lysis *in vitro*. He noted, too, that the red cells of the experimental animal became more fragile to osmotic hæmolysis in hypotonic saline, and discussed possible causes of this; he apparently rejected the hypothesis, which he attributed to Widal, that the increased fragility was due to adsorbed amboceptor—that is antibody—and considered that the change more probably resulted from a peculiar "fragilizing activity" which the animal possesses or develops, and that the severe anæmia which a hæmolytic serum might produce after injection was in large part due to the hæmolytic activity or potentiality of the animal itself.

Banti then considered where this hypothetical hæmolytic potentiality was likely to be located, and concluded that the spleen was in fact the most important organ in this respect. Firstly, he noted that when hæmolytic sera were given to splenectomized animals the resistant

effects were less intense; there was less anæmia, and this occurred more slowly; osmotic fragility changes were less marked and there was less hæmoglobinæmia. Secondly, he referred to the well-known fact that the spleen enlarges after the administration of serum and becomes greatly congested. He described how the red cells fill the sinuses and infiltrate the pulp cords in large numbers. He pointed out that the endothelial cells become swollen and act as erythrophages; and that within the pulp are agglutinated masses of cells, some lacking hæmoglobin but others being well-filled small cells. Banti added, significantly, that with large doses of serum the liver shows rather similar changes; the capillaries are dilated and packed with agglutinated cells and the Kupffer cells act as erythrophages. Banti was a most acute observer; almost everything he reported has, in retrospect, been shown to be correct.

I shall now pass from Banti (1913) to Dameshek and Schwartz (1938*b*) of Boston. Little seems to have been accomplished during the intervening twenty-five years. The monograph of Pearce *et al.* (1918) is a useful source of information but their own experiments with hæmolytic sera do not seem to have really advanced the subject further than had Muir and McNee and Banti.

*Recent studies.*—Dameshek and Schwartz (1938*b*) reopened the whole question. They repeated the experiments of earlier workers, related the microspherocytosis, illustrated by Muir and McNee, to increased osmotic fragility, demonstrated by Banti, and stressed the relationship between the dosage of serum and the intensity of the hæmolysis which resulted; and finally they emphasized the very close similarity of acquired hæmolytic anæmia in man with the hæmolytic syndromes produced in animals as the result of the administration of hæmolytic sera. This is the great merit of their work; they stimulated interest in acquired hæmolytic anæmia and put it firmly on the map as an antibody-induced disease. Dameshek and Schwartz, however, over-emphasized the similarity between the experimental disease and the disease in man.

Bessis and Freixa (1947) worked with rats, from one day old to 4 months of age. They demonstrated several important points: for instance, they found that hæmolysis would follow the administration of antiserum given by mouth to rats in the neonatal period; they found, too, that it was impossible to produce a chronic anæmia by continuing the administration of the antiserum and deduced from this that the recipient animal in turn might produce antibodies against the administered antiserum. They also described the sequence of morphological changes affecting the red cells in considerable detail; in particular, they described as an early effect, before spherocytosis, the tendency of the red cells to become sticky so that, when subjected to strain, as might be produced by pressure on a coverslip overlying a suspension of red cells in serum, cells "en fuseaux" are produced. The same phenomenon of elongated red cells linked together almost by a thread may be seen in human cases of acquired hæmolytic anæmia.

The role of the spleen in experimental hæmolytic anæmia has been re-studied by several groups of workers using rats, dogs and guinea-pigs (Franke, 1950; Piovella and Formaggio, 1950; Tischendorf and Franke, 1950–51; Wasastjerna, 1951; Piovella, 1953). The general conclusion has been that prior splenectomy has little or no influence on the progress of hæmolysis in rats, but in dogs and guinea-pigs the operation is protective to some extent.

Further studies have also been carried out on the immunity which seems to develop in animals given repeated injections—this was suspected by Muir and McNee as well as by Bessis and Freixa. Samaille and co-workers in 1953 working with dogs (Samaille *et al.*, 1953; Samaille and Richardson Jones, 1953) have shown that the recipients' corpuscles normally become coated with their own serum globulin, in addition to heterologous protein, in the course of the response to the injection of the immune serum, and that this process is intensified and hæmolysis inhibited in animals previously immunized to the protein of the species providing the hæmolytic immune serum. Davidsohn and co-workers (1957) more recently have carried out similar experiments in rabbits.

Another aspect of hetero-antibody activity is its action on red-cell precursors in the bone-marrow. Linke in 1952, working with rats, showed that bone-marrow damage leading to reticulocytopenia frequently follows the administration of hæmolytic serum. The interest of this finding is that it parallels the observation of aplastic episodes during the course of acquired hæmolytic anæmia in man.

Finally, direct observation of transilluminated vessels has shown, in the hamster, actual auto-agglutination occurring in the recipient's circulating blood after the administration of hæmolytic immune serum (Wasastjerna *et al.*, 1954).

### *Experimental Work in Animals Using Iso-immune Sera*

Lawrence Young and his colleagues have studied the action of iso-antibodies on incompatible red cells in dogs. This work is particularly significant because it has provided data on the comparative effects of antibodies *in vitro* and *in vivo*, and for demonstrating that antibodies themselves vary qualitatively in their ability to bring about red-cell destruction and that red cells, too, vary in their sensitivity to damage.

The work of Lawrence Young's group on dogs is summarized in a paper by Scott Swisher and Young (1954). They showed that an iso-antibody, anti-A, which was potent in producing lysis *in vitro*, caused rapid lysis *in vivo* of canine $A_1$ cells, and marked hæmoglobinæmia. As in the experimental animal receiving heterologous serum, intravascular lysis was thus the principal mechanism of cell destruction. With $A_2$ cells, however, which canine anti-A does not lyse *in vitro*, hæmolysis was much slower *in vivo*, although some degree of intravascular destruction occurred. Canine anti-B -C or -D agglutinated the corresponding cells under laboratory conditions at 37° C., although not lysing them; but they did not cause appreciable cell destruction *in vivo* in the concentrations present in the experimental animal. They were also able to demonstrate a progressive increase in the rate of hæmolysis when incompatible cells were administered to a dog whose serum neither agglutinated nor lysed them *in vitro*, although it did eventually sensitize the donor's cells to an antiglobulin serum.

In some ways the work of Young and his colleagues provides a closer parallel to the spontaneously-occurring human disease than does the animal work I have referred to. The reason is that immune sera obtained by immunizing animals with the red cells of another species are agglutinating antibodies, which are also lytic *in vitro*, at lower titres, in the presence of complement. In animals this type of antibody certainly gives rise *in vivo* to intravascular lysis leading to hæmoglobinæmia. In man, on the other hand, an agglutinating and hæmolytic antibody, active at 37° C., is the rarest of all the antibodies which may be associated with acquired hæmolytic anæmia. Indeed, there is, in the literature dealing with the human disease, no full and detailed description of the behaviour of an antibody with these characteristics. Hence, the probable mechanisms of hæmolysis in the experimental animal, namely actual dissolution of red cells through the action of antibody and complement, auto-agglutination in the circulation, with trapping of the agglutinates in the spleen and liver capillaries, and elsewhere, followed by erythrophagocytosis, spherocytosis and the filtering off of spherocytes by the spleen, are not necessarily applicable to the human disease.

The production by Young and his co-workers of hæmolysis after the administration of a serum which neither agglutinated nor lysed the recipient's cells *in vitro*, but did destroy them *in vivo*, seems on the other hand to be closely analogous to the most common type of situation in man and it brings us to the crux of the whole question: How does so-called "incomplete" antibody, be it either iso- or auto- in type, which does not cause agglutination or lysis under laboratory conditions, bring about red-cell destruction in a living subject?

### *Hæmolysis Due to Incomplete Antibodies*

Red cells coated by incomplete antibodies may undergo auto-agglutination when suspended in human serum at 37° C. This phenomenon seems likely to be akin to so-called "conglutination", as described by Wiener (1945) in relation to hæmolytic disease of the newborn. Jandl and Castle (1956) have shown that the presence of several macromolecular substances, including human serum proteins in concentrations only slightly exceeding the physiological levels, and polyvinylpyrrolidone (PVP), causes the agglutination of red cells previously sensitized with incomplete (or "coating") antibodies. Of plasma proteins, fibrinogen and gamma globulin were most effective and albumin least effective, whilst PVP seemed likely to be useful in demonstrating abnormal auto-agglutinability of red cells in patients with acquired hæmolytic anæmia at a time when the antiglobulin test was negative or only weakly positive.

Using normal concentrations of plasma proteins the agglutinates produced are smaller and more like rouleaux, but these, too, resist dispersion in saline. Cells "en fuseaux", as described by Bessis and Freixa (1947), can be produced by pressure on the coverslip.

Jandl and Castle suggest that it is the action of plasma proteins on cells sensitized by incomplete antibodies causing them to form unusually adherent rouleaux or small agglutinates that may be responsible for the trapping of the cells in the spleen and elsewhere. Moreover, a local increase in plasma protein concentration has been thought perhaps to occur in the spleen, and might be expected to agglutinate cells not agglutinated in the general circulation.

This seems to me to be a reasonable hypothesis, and in human cases it is not unusual to find small clumps of agglutinated cells which resist dispersion when blood is diluted in the course of a red-cell count.

Jandl *et al.* (1957) have, in a more recent paper, expanded these views; in particular, they stress the demonstrable occurrence of agglutinated red cells in films made of blood obtained from the spleen pulp at the time of splenectomy for acquired hæmolytic anæmia. They concluded that cell destruction follows sequestration of red cells in the pulp within a few minutes and that the released hæmoglobin is converted to bilirubin within 1–2 hours. The exact mechanism by which the sequestered cells are destroyed is not yet understood. Certainly, erythrophagocytosis is one such mechanism, but it seems doubtful whether this can be the whole story.

### *Mechanism of Production of Spherocytosis*

I now come to the possible mechanisms for the occurrence of the spherocytosis which so frequently accompanies acquired hæmolytic anæmia. Both agglutinating and incomplete antibodies seem capable of provoking the change. In essence, it is a transformation of disc-like cells towards a spherical form, with contraction of their surface area but with little or no shrinkage in volume. In the experimental animal it regularly occurs within a few hours of the administration of serum; in man it is a variable feature, but its intensity, in a particular patient, usually parallels the clinical course of his disease. It has long been known (since before Banti's time) that antibodies, while causing increased red-cell osmotic fragility—a reflection of spherocytosis—in some way in the living animal or in man, do not do this under ordinary laboratory conditions *in vitro*. It is also known that spherocytosis can occur perfectly well in the experimental animal or in man in the absence of the spleen.

Castle *et al.* (1950) presented experimental evidence which suggested that spherocytosis might be brought about by antibody action in the following way: auto-agglutination in the peripheral blood might lead to sequestration of red cells in tissue capillaries and an increased concentration of the cells in their plasma; the resultant blocking of capillaries might then lead to ischæmic injury of tissue cells with release of substances that increase the osmotic and mechanical fragilities of the red cells locally. Subsequently, the red cells lysed or escaped into the blood stream as spherocytes.

Castle *et al.* seem to have clearly demonstrated a possible mechanism, but it has yet to be shown whether this is the complete answer. It is possible to conceive, as an alternative hypothesis, that red cells coated with antibodies might have their metabolism injuriously affected, either directly or indirectly. Evidence in favour of this hypothesis has in fact been provided by Selwyn (1953) and Young and co-workers (1956) who demonstrated that glucose added to red cells from patients with acquired hæmolytic anæmia with spherocytosis might fail to diminish the rate of spontaneous hæmolysis as it normally does when the blood is incubated *in vitro*. In accord with this hypothesis, too, were some observations of Swisher, Young and Prankerd (Swisher and Young, 1954). They found that the red cells of an A+ dog, transfused with canine plasma containing anti-A, behaved abnormally in respect of the uptake *in vitro* of radiophosphorus. More recently, Storti *et al.* (1956) have reported that the rate of glycolysis of red cells to which incomplete anti-D serum has been added *in vitro* is diminished by a factor of about one-quarter; they suggest that the lower energy production, of which the observable diminished glycolysis is a feature, may be a factor in determining the diminished life-span of antibody-sensitized cells *in vivo*.

### *Observations on Human Cases of Acquired Hæmolytic Anæmia*

*Warm antibodies.*—I shall, for the moment, only talk about patients who have formed auto-antibodies active at body temperature, i.e. so-called "warm" antibodies. This approach has its limitations. First, we have to accept the fact that there is no easy way of assessing, in the laboratory, the degree to which red cells are damaged by being coated with antibodies. Although, if we carry out the direct antiglobulin test, the presence of strongly-reacting cells is often associated with rapid hæmolysis *in vivo*, this is not always so; moreover, in some patients rapid hæmolysis may occur when the red cells appear only to be weakly sensitized with antibodies or even when the antiglobulin test gives negative results. Nor can spherocytosis be clearly correlated with rates of hæmolysis *in vivo*; here though, it is true to say that if marked spherocytosis is present, the patient is usually hæmolysing rapidly. There is, on the other hand, a correlation between the presence of free antibody in the patient's serum, which is probably a reflection of excessive antibody formation, and severe anæmia, but even here there are exceptions.

These facts suggest that there are subtle differences in the auto-antibodies produced by individual patients which are not easily assessed by laboratory tests and that there must be other variable factors which are difficult to measure, such as the activity of the R.E. system, that play a part in determining rates of hæmolysis and hence the clinical state of the patient.

The rather unpredictable effect of splenectomy, which is by no means necessarily of great benefit to the patient, clearly demonstrates that organs other than the spleen may be important in hæmolysis. Human patients, however, often seem to be benefited to a greater extent by splenectomy than is the experimental animal given hæmolytic immune sera.

*Effect of splenectomy in man and the experimental animal.*—How can the generally more beneficial effect of splenectomy in man than in the experimental animal be explained, if the two conditions are in fact analogous? There are, of course, differences between the two. Firstly, it is conceivable, and indeed likely, that the spleen itself in man is a site of antibody formation. However, I doubt whether this is an important point; indeed, I am not aware of any evidence in favour of its being a major source of antibody. One of the difficulties in trying to establish this point in man is that in patients who have warm antibodies in their serum the amount of free antibody in the serum is usually so small that it is difficult or impossible to titrate it quantitatively with any accuracy. Another difficulty, as I have already mentioned, is that it seems to be doubtful whether it is justifiable to equate the intensity of the agglutination of patients' red cells by an antiglobulin serum with the amount of antibody formed. I have, however, one detailed observation on a patient who had developed a rather peculiar cold antibody of relatively high thermal amplitude; this shows quite clearly that antibody formation proceeded unaltered after operation, despite the fact that the mean life-span of transfused normal red cells increased from 11·5 days to 26 days (Dacie, 1954, Case 13). In this patient, at least, the spleen was clearly acting as a hæmolytic organ rather than as an important source of antibody.

The second difference between the experimental animal and man lies, as I have already mentioned, in the type of antibody formed. There is now good evidence that antibodies which are powerfully lytic *in vitro*, as well as being agglutinating, cause rapid lysis of red cells within the blood stream *in vivo* if present in sufficient concentrations, both in man and in the experimental animal. Hæmolysis within the spleen is of minor importance. If the antibody is weakly lytic, hæmolysis within the blood stream is less important, and the bulk of the affected cells form small agglutinates which are filtered off by the liver, and probably by other organs too, as well as by the spleen. However, the spleen is still of minor importance in hæmolysis. This has been shown to be the case in man, using iso-antibodies like anti-A and incompatible cells, by Jandl *et al.* (1957) and by Cutbush and Mollison (1958). Both groups of workers have used radiochromium-tagged cells and followed their fate by surface counting. Incomplete non-agglutinating and non-lytic antibodies, such as anti-D, on the other hand, seem to produce cell destruction chiefly by bringing about trapping of cells within the spleen. Even so, evidence was found that cells heavily coated with incomplete antibodies were also removed from the blood stream to a greater or lesser extent by the liver.

These observations closely parallel what has been observed in connexion with auto-antibodies in human acquired hæmolytic anæmia. Although Chertkow and Dacie (1956), in reviewing the results of splenectomy, concluded that most patients were benefited to some extent by the operation, it was when the rate of hæmolysis was the greatest, i.e. at a time when the patient was producing a great deal of antibody, that splenectomy was particularly ineffective. The few patients who produce an agglutinating type of antibody active at 37° C. are in a most serious state, and splenectomy then may not help at all. In one such patient of my series, fatal fulminating hæmolysis developed years after splenectomy had been carried out (Dacie, 1954, Case 12). No splenunculi were demonstrable.

The results of $^{51}Cr$ studies in man suggest that it may be possible, by *in vivo* surface counting, to predict whether or not splenectomy will be useful, basing this opinion on whether there is a high uptake of chromium, derived from effete corpuscles, in the spleen or whether this uptake is shared by the liver (Jandl *et al.*, 1956; Hughes Jones and Szur, 1957). I think it will be found, when further data are available, that, although the spleen is normally considerably more active than is the liver in the removal of cells sensitized by incomplete antibodies, the liver itself is not entirely passive. In support of this view is the fact that, in patients who fail to respond to splenectomy, this is often associated with engorgement of the liver with blood, and it appears that the liver is to some extent taking the place of the spleen.

*Cold antibodies.*—The patients who form cold antibodies of relatively high thermal amplitude can be grouped into three main disease syndromes: (1) acute hæmolytic anæmia following virus pneumonia; (2) the "cold hæmagglutinin syndrome", a disorder of unknown origin, affecting elderly subjects, and comprising chronic hæmolytic anæmia with Raynaud's phenomena and hæmoglobinuria in cold weather; and (3) hæmolytic anæmia associated with

lymphosarcoma or reticulosarcoma. I believe the mechanism of hæmolysis to be the same in patients belonging to each of the above groups.

A view widely held at one time, and particularly stressed by Stats (1945), was that the hæmolysis was due to abnormal mechanical fragility of tightly agglutinated masses of red cells. It is, indeed, easy to show that manhandling of the blood of such patients at room temperature readily brings about hæmolysis. However, it was soon apparent that hæmolysis *in vivo* could not in fact be closely associated with the agglutinin titres as measured in the laboratory by conventional means at 2–4° C. Ham *et al.* (1948) concluded that mechanical trauma caused lysis only when the corpuscles were already sensitized by incomplete antibodies. They studied two patients whose sera contained cold agglutinins at similar titres in the cold; in one patient there was clinical evidence of hæmolysis and his red cells gave a positive antiglobulin test; the other patient was convalescing from virus pneumonia—she was not anæmic and her cells gave a negative antiglobulin test. Chilling the patients' arms for 20 minutes produced hæmoglobinæmia in the first patient (whose cells were sensitized) but not in the second.

The viewpoint that mechanical trauma plus coating of the corpuscles is required for hæmolysis does not strike me as an adequate explanation. I believe that there are two factors which determine whether there will be abnormal hæmolysis *in vivo*; the thermal range of the antibodies, and their ability to bind on complement. The thermal range of the antibody is of major importance. In patients with active hæmolysis *in vivo* agglutination is usually demonstrable *in vitro* up to temperatures of 28°–32° C.—if the antibody is inactive at this temperature range the patient will usually be found to be free from excess hæmolysis unless he exposes himself to an unusual degree of chilling.

These observations fit in well with what is known of the skin and subcutaneous temperatures in man. Barcroft and Edholm (1946) have shown that the subcutaneous temperature of the bared forearm will readily fall below 30° C. when the forearm is exposed to air at 18·5° C., that is to say, to rather cool room temperature. It is thus reasonable to suppose that a certain amount of transient auto-agglutination will continuously be taking place in the skin vessels of patients living in temperate climates whose sera contain high-thermal-amplitude cold antibodies. Evidence that this is so is the persistent presence of positive direct antiglobulin reactions given by the blood of these patients. Such reactions are a reflection of union of antibody with cells leading to the irreversible attachment of complement (Dacie *et al.*, 1957).

Over and above the continuing sensitization of the patient's red cells, there are the events which occur in cold weather. The skin temperature of certain areas, particularly that of the toes, fingers, ears and tip of the nose, drops; more massive agglutination sets in in the cutaneous vessels and this leads to further cooling of the part, more intense agglutination and visible cyanosis—Raynaud's phenomena. Hæmoglobinæmia occurs and often hæmoglobinuria.

Whether the gross intravascular hæmolysis leading to hæmoglobinuria is due to the disintegration of tightly packed cells (the mechanical fragility effect) or due to lysis by complement is uncertain. It would seem probable that both mechanisms occur; it is, however, my impression that intravascular hæmolysis is more evident in those patients who have sera which are relatively active in causing hæmolysis in the laboratory. However, it is difficult to be certain about this, as hæmolytic activity and high thermal amplitude, which is clearly of paramount importance, often seem to go together.

In rare cases, agglutination *in vitro* due to cold antibodies may take place at temperatures almost reaching 37° C. Such patients develop severe hæmolytic anæmia, irrespective of the ability of the antibody to cause actual lysis in the laboratory. One such case was a woman with widespread reticulosarcoma. Her serum contained a non-lytic auto-agglutinin of moderate titre (1024 at 2° C.). Its activity, however, stretched up to about 35° C. Splenectomy seemed to have absolutely no effect on hæmolysis, and she died from uncontrollable anæmia.

We have recently studied, using radiochromium, red-cell survival in two patients with the cold hæmagglutinin syndrome. In each case surface counting showed that chromium was taken up by the liver to about the same extent as by the spleen (Lewis *et al.*, 1958). This suggests that splenectomy would be ineffective. The operation has in fact seldom been carried out on such patients, but I know of one report of its being a failure (Baumgartner, 1955).

I have not considered the effect of steroid therapy on either experimental or human acquired hæmolytic anæmia. Firstly, I wished to constrict this already too rambling address, and secondly, because I do not feel that the use of steroids has helped us much in our understand-

ing of the pathogenesis of the hæmolysis. However, the often reported failure of steroid hormones to influence the course of the experimental disease (*see* Dacie, 1954), compared with the frequent success of their use in human acquired hæmolytic anæmia, further underlines the differences between the two types of hæmolytic processes.

## REFERENCES


Banti, G. (1913) *Sem. médica, Paris*, **33**, 313.
Barcroft, H. and Edholm, O. G. (1946) *J. Physiol.*, **104**, 366.
Baumgartner, W. (1955) *Schweiz. med. Wschr.*, **85**, 1157.
Belfonti, S., and Carbone, T. (1898) *G. Accad. Med. Torino*, ser. 4, **46**, 321.
Bessis, M., and Freixa, P. (1947) *Rev. Hémat.*, **2**, 114.
Boorman, K. E., Dodd, B. E., and Loutit, J. F. (1946) *Lancet*, i, 812.
Bordet, J. (1898) *Ann. Inst. Pasteur*, **12**, 688.
Cantacuzène, J. (1900) *Ann. Inst. Pasteur*, **14**, 378.
Castle, W. B., Ham, T. H., and Shen, S. C. (1950) *Trans. Ass. Amer. Phycns.*, **63**, 161.
Chauffard, M. A., and Vincent, C. (1909) *Sem. médica, Paris*, **29**, 601.
Chertkow, G., and Dacie, J. V. (1956) *Brit. J. Hæmat.*, **2**, 237.
Coombs, R. R. A., Mourant, A. E., and Race, R. R. (1945) *Brit. J. exp. Path.*, **26**, 255.
Cutbush, M., and Mollison, P. L. (1958) *Brit. J. Hæmat.*, **4**, 115.
Dacie, J. V. (1954) The Hæmolytic Anæmias. London.
——, Crookston, J. H., and Christenson, W. N. (1957) *Brit. J. Hæmat.*, **3**, 77.
——, and Mollison, P. L. (1943) *Lancet*, i, 550.
Dameshek, W., and Schwartz, S. O. (1938*a*) *New Engl. J. Med.*, **218**, 75.
——, —— (1938*b*) *Amer. J. med. Sci.*, **196**, 769.
——, —— (1940) *Medicine, Baltimore*, **19**, 231.
Davidsohn, I., Hermoni, D., and Hanawalt, E. G. (1957) *Blood*, **12**, 710.
Dudgeon, L. S., Panton, P. N., and Ross, E. A. (1908) *Proc. R. Soc. Med.*, **2**, Sect. Path., 64.
Franke, R. (1950) *Folia hæmat., Lpz.*, **70**, 189.
Ham, T. H., Gardner, F. H., Wagley, P. F., and Shen, S. C. (1948) *J. clin. Invest.*, **27**, 538.
Hayem, G. (1898) *Pr. méd.*, **6**, 121.
Hughes Jones, N. C., and Szur, L. (1957) *Brit. J. Hæmat.*, **3**, 320.
Jandl, J. H., and Castle, W. B. (1956) *J. Lab. clin. Med.*, **47**, 669.
——, Greenberg, M. S., Yonemoto, R. H., and Castle, W. B. (1956) *J. clin. Invest.* **35**, 842.
——, Richardson Jones, A., and Castle, W. B. (1957) *J. clin. Invest.*, **36**, 1428.
Kraus, R., and Sternberg, C. (1902) *Zbl. Bakt.*, **32**, 903.
Levaditi, C. (1902) *Ann. Inst. Pasteur*, **16**, 233.
Lewis, S. M., Szur, L., and Dacie, J. V. (1958) To be published.
Linke, A. (1952) *Verh. dtsch. Ges. inn. Med.*, **58**, 724.
Muir, R., and McNee, J. W. (1911–12) *J. Path. Bact.*, **16**, 410.
Pearce, R. M., Krumbhaar, E. B., and Frazier, C. H. (1918) The Spleen and Anæmia. Experimental and Clinical Studies. Philadelphia.
Piovella, C. (1953) *Hæmatologica*, **37**, 367.
——, and Formaggio, T. G. (1950) *Hæmatologica*, **34**, 693.
Samaille, J., and Richardson Jones, A. (1953) 4th Congress of European Society of Hæmatology. Amsterdam.
——, Ropartz, C., and Eyquem, A. (1953) *Ann. Inst. Pasteur*, **85**, 48.
Selwyn, J. G. (1953) Unpublished observations.
Stats, D. (1945) *J. clin. Invest.*, **24**, 33.
Storti, E., Vaccari, F., and Baldini, E. (1956) *Experientia*, **12**, 108.
Swisher, S. N., and Young, L. E. (1954) *Trans. Ass. Amer. Phycns.*, **67**, 124.
Tischendorf, W., and Franke, R., (1950–51) *Z. ges. exp. Med.*, **116**, 92.
Wasastjerna, C. (1951) *Acta med. scand.* Suppl. 258.
——, Pisciotta, A., and Dameshek, W. (1954) *Acta med. scand.*, **148**, 173.
Widal, F., Abrami, P., and Brulé, M. (1908*a*) *Arch. Mal. Coeur*, **1**, 193.
——, ——, —— (1908*b*) *C.R. Soc. Biol., Paris*, **64**, 655.
——, ——, —— (1909) *Bull. Soc. méd. Hôp. Paris*, **28**, 73.
Wiener, A. S. (1945) *J. Lab. clin. Med.*, **30**, 662.
Young, L. E., Izzo, M. J., Altman, K. I., and Swisher, S. N. (1956) *Blood*, **11**, 977.

# Section of Dermatology

President—JOHN T. INGRAM, M.D., F.R.C.P.

[*April* 17, 1958]

**Angiokeratoma Corporis Diffusum.**—H. J. WALLACE, M.D.

Mr. A. A., aged 36.

Angiokeratoma corporis diffusum since childhood. No sensible sweating. Bilateral ulceration of legs. Superficial dystrophic corneal changes; moderate albuminuria and impairment of tubular function.

Renal biopsy: Doubly refractile vacuolation of epithelial cells of glomeruli, occasional cells of Bowman's capsule and in many cells in the ascending loops of Henle and distal tubules with sparing of proximal tubules. These changes are thought to be specific to this disease in an early or moderately advanced stage. Similar vacuolation in arterioles in skin and kidney. No cause found for impairment of sweating. Similar renal and other changes in mother and cousin. Mother said not to have had rash.

**Ectodermal Defect with Skeletal Abnormalities.**—E. WILSON JONES, M.R.C.P. (for H. J. WALLACE, M.D., F.R.C.P.).

Miss J. P., aged 22, presented with a scabies infestation.

*Past history.*—The patient sustained burns on her hands at the age of 2 years as the result of a fall into a fire, and she ascribes her present deformed and scarred hands to this event. Her facial appearance has always been abnormal due to failure of development of her upper jaw and teeth. In 1955 and 1956 she had two plastic operations with bone grafting, in which an attempt was made to fill out her sunken cheeks. At the same time several hypoplastic teeth were removed. She sustained a fracture of the left tibia at the age of 10. Her menstruation started at the age of 15 and has been regular since, yet in spite of this evidence of sexual maturity, her breasts have failed to develop. She denies any trouble with the skin apart from scabies. She maintains that she sweats normally and has never suffered from heat intolerance, and is able to work in a laundry without difficulty. We were unable to interview the relatives to obtain an independent history of her condition in infancy and childhood.

*Family history.*—Her mother and father and 11 siblings (6 sisters, 5 brothers) are all said to be normal. None have deformities or complain of inability to sweat. No consanguinity.

*On examination.*—Her facies is striking. The central portion of her face is relatively underdeveloped. The cheeks, upper jaw and nose are sunken, giving the so-called inverted dish-shaped deformity reminiscent of congenital syphilis. The eyes are a little prominent. The skin is thin and fine and rather dry, and on her back it has a translucent appearance with superficial veins showing through. There is also a very fine light granular pigmentation. The scalp hair is a little coarse but otherwise probably normal. The eyebrows and pubic hair are normal, but her axillary hair is very sparse. The nails on both hands and feet are poorly developed and foreshortened. There is no development of breast tissue. The nipples are rudimentary.

*Skeletal system.*—There is a severe bilateral flexion deformity of the digits of both hands, causing marked limitation of finger movements. The defect appears to be due to scarring and contracture of the subcutaneous tissue and skin. The feet are also affected in a similar manner but to a lesser degree, there being some foreshortening and pes cavus with contraction of the toes. Her knees are large and knobbly, with slight subluxation backwards of the tibia on the femur, but there is, however, only slight limitation of joint movement. The tibiæ themselves show backward bowing. The palate is narrow and vault-shaped and she is edentulous. The remainder of her skeleton is normal. On general medical examination nothing else of note was discovered. Her blood pressure was 130/90. She is a person of low intelligence.

*Investigations.*—X-rays: Skull: Agenesis of maxilla mainly of the premaxillary part. There were large numbers of unerupted teeth both in the maxilla and in the mandible.

Hands: Short metacarpal bones with some absorption of the terminal tufts of the distal phalanges. Severe flexion deformity.

Knees: Poorly developed cortex with some widening of the bone ends.

17-Ketosteroids: daily output 3·6 mg. Second estimation 8·3 mg.

*Comment.*—This patient's condition is probably a variant of the anhydrotic ectodermal defect as described by Clouston (1939), Upshaw and Montgomery (1949) and others. It is unusual to get this syndrome in females as the defect is usually inherited as a sex-linked recessive and is thus limited to the male sex. Cases described in females are probably due to a different mode of inheritance.

The absence of breasts in association with ectodermal defect has only been recorded occasionally. Osbourn in 1952 reviewed the literature and could only find 5 cases, all of whom were, surprisingly enough, of the male sex.

The occurrence of skeletal deformities has been noted by Montgomery without giving any details. Pilsbury *et al.* (1956) published a photograph of a case with a very similar flexion deformity of the hands in a woman. The contracture of our patient's hands might be accounted for by her burns. This is, however, unlikely as the deformity is bilateral and symmetrical and is also affecting her feet.

We felt that it might well have been possible to demonstrate some defect in her sweating, but the patient would not permit this investigation.

REFERENCES

CLOUSTON, H. R. (1939) *Canad. med. Ass. J.*, **40**, 1.
OSBOURN, R. A. (1952) *J. Amer. med. Ass.*, **148**, 644.
PILSBURY, D. M., SHELLEY, W. B., and KLIGMAN, A. M. (1956) Dermatology. Philadelphia and London; p. 1207.
UPSHAW, B. Y., and MONTGOMERY, H. (1949) *Arch. Derm. Syph., Chicago*, **60**, 1170.

**Dr. E. Lipman Cohen:** Has it been confirmed that she is a true biological female?

**Dr. Wilson Jones:** No.

**The President:** The hands remind me of a child I saw with epidermolysis bullosa. The hands had been bandaged for years and became one mass of soft tissue. There is no suggestion of epidermolysis bullosa in this case?

**Dr. Wilson Jones:** No.

**Eczema With Acantholytic Bullæ.**—H. T. H. WILSON, M.R.C.P.

Mrs. M. C., aged 27. Housewife.

*History.*—Four years ago she developed a red rash on the front of the right wrist. This gradually spread to involve the flexural surfaces of both arms, and the sides of the neck and the face. She attended several dermatologists and her condition was variously diagnosed "eczema", "contact dermatitis", "neurodermatitis" or "seborrhœic dermatitis". Improvement was succeded by relapse on each occasion.

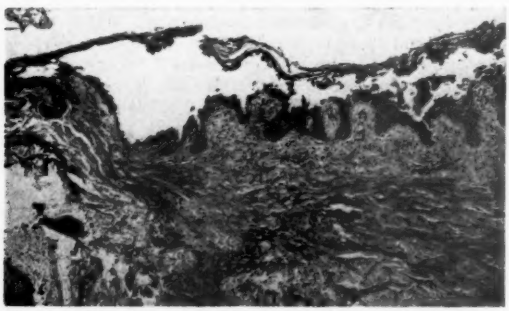


FIG. 1.—Section showing intra-epidermal bulla with acantholysis

On 24.11.56 she developed a blister on the right shoulder. This burst and left behind it a red scaling patch. In the course of the next ten days she developed blisters over most of the body surface (Fig. 2). Scaling patches, mostly round, but some circinate were left behind after rupture of the blisters (Fig. 3). No abnormality was discovered on general examination. A clinical diagnosis of pemphigus foliaceus was made and supported by the finding of unmistakable acantholysis on histological examination of an intact vesicle (Fig. 1). During the next week several lesions became pustular and she had a temperature of 102° F.

19.12.56: Treatment was begun with ACTH 20 units b.d. The following day she was afebrile, two days later all the blisters had begun to dry up and no fresh ones had appeared. 24.12.56: ACTH was stopped and she was allowed to go home.

28.12.56: The skin was clear except for a number of scabs on the trunk. 15.2.57: There was a recurrence of itching and erythema on the arms and she was given prednisone 5 mg. t.d.s. during February and March. In April the dose was reduced to 5 mg. b.d. and it was discontinued in May 1957.

Since then an itching, apparently eczematous, eruption has persisted on the neck and arms but there have been no further blisters.

*Past history.*—No serious illnesses.

*Family history.*—Irrelevant.

*Investigations.*—Biopsy 14.12.56 (Dr. R. A. B. Drury): There is a split in the superficial prickle-cell layer of the epidermis, which shows definite acantholysis. This bleb contains acantholytic cells and neutrophils, but few eosinophils. There is a diffuse leucocytic infiltrate of mixed type in the superficial corium. The acantholysis suggests that this is pemphigus.



FIG. 2.—Bullæ on trunk and arms.



FIG. 3.—Buttocks showing bullæ and scaling patches.

Biopsy 10.1.57 (Dr. H. Haber): There is an acantholytic process as seen in pemphigus.

Biopsy 15.1.58 (Dr. Drury): Skin biopsy showing some small areas of parakeratosis, but no other abnormality and no evidence of acantholysis.

Swab from pustule 4.12.56: Pus cell ++, Gram-positive cocci ++, Culture *Staph. pyogenes* +++.

6.12.56: Hb 100%. W.B.C. normal.

10.12.56: Slight neutrophilia.

**Dr. H. Haber:** This case shows clinically eczema with a superimposed erythema multiforme. The latter condition may show histologically subcorneal acantholysis looking like pemphigus foliaceus. Acantholysis is not confined to the pemphigus group only. One has to be very careful to diagnose pemphigus histologically by finding acantholysis.

Whereas pemphigus is due to an acantholytic process, non-acantholytic bullæ may occasionally be seen in true pemphigus. On the whole I would say that there is no pemphigus without acantholysis, but there may be acantholysis without pemphigus.

**Dr. C. H. Whittle:** She was going through a period of considerable stress in the first attack and I wondered if she had been given any sedative which might have been responsible for this type of reaction.

**The President:** I wondered whether she might have dermatitis herpetiformis which can present in an eczematous pattern; she has had periods of intense and intolerable itching and it might be precipitated by a state of stress.

**Dr. Wilson:** She was not having any drugs at the time when the bullæ appeared. We did not think of the possibility of dermatitis herpetiformis, but it would be interesting to try the effect of dapsone.

**Multiple Sebaceous Papillomas.**—P. A. J. SMITH, M.B., M.R.C.P.

Mr. A. G., Maltese, aged 34. Steward.

*History.*—Since 1954 small warts and blackheads have been appearing on the face and forehead. He presented for treatment at the London Hospital four months after their onset and has since attended irregularly. The lesions grow slowly, rarely exceed 3 mm. in height or diameter. One on the nose reached a diameter of 1 cm. in three months and clinically was typical of a kerato-acanthoma.

*Family history.*—He does not think other members of his family have any similar condition.

*On examination.*—Sites: Forehead, nose, nasolabial folds. Lesions: Dome-shaped, skin-coloured papules up to 3 mm. in diameter, some with depressed centres resembling molluscum contagiosum; others with warty centres suggestive of molluscum sebaceum; yet others appear to be filiform warts.

*Histology.*—Most lesions are squamous cell papillomas with horny plugging of follicles and sebaceous hyperplasia. The sebaceous cells are continuous with the prickle cells and form part of the papilloma.

*Comment.*—If the term "molluscum sebaceum" were not used synonymously with "kerato-acanthoma" it would be appropriate for these lesions, many of which grossly resemble kerato-acanthoma. Microscopically they differ in that the central horny plug is surrounded by sebaceous rather than prickle cells; in fact true sebaceous mollusca.

**Dr. H. Haber:** Dr. Smith's case shows multiple papillomatous tumours which show histologically a peculiar picture. There is marked acanthosis and downgrowth of the epidermis. The cells of the acanthotic areas, however, show differentiation into mature sebaceous gland cells. I have seen a case of similar histology, but this case showed a solitary tumour which in its clinical and histological structure showed the features of kerato-acanthoma, but here again the acanthotic cells were all sebaceous gland cells. This is the only case, I think, which would qualify for the term "molluscum sebaceum."

**Generalized Nævoid Pigmentation.**—E. WILSON JONES, M.R.C.P. (for H. J. WALLACE, F.R.C.P., and R. J. CAIRNS, M.R.C.P.)

J. P., girl aged 4.

*History.*—The skin was first noticed to be abnormal at about the age of 13 months. At that time the pigmentation started on the abdomen and gradually spread to involve the skin generally: it has become progressively deeper until the past few months, since then there has been no change.

Her birth weight was 4 lb. 12 oz. She was a full-term infant after a normal pregnancy and a normal delivery. She has always been underweight, but has passed the normal milestones, sitting up at the age of 6 months and walking at the age of 15 months. She has never had any serious illnesses or symptoms of ill-health to account for her under-development.

*Family history.*—Only child; normal parents of English descent. No history of pigmentation. No consanguinity.

*On examination.*—Small, frail, alert child (weight 24 lb.—10 lb. under average weight). The skin throughout was deeply pigmented, varying in colour from a deep brown to a steely grey. The pigmentation was mottled and most marked in the axillæ and on the flanks and tended to be less marked on the face and other exposed areas. In all areas there were numerous, small, round to oval macules of paler pigmentation, thus giving an over-all raindrop effect. The skin was of normal texture and elasticity. The nails, hair and mucous membranes were normal, and no abnormality was found in the eyes. She had a peculiar facies, the features being rather pinched and giving a bird-like effect. Her hands were on the small side. The fifth fingers were abnormally short and curved. On general medical examination there was nothing of note other than a soft systolic murmur in the pulmonary area of the heart. This murmur is probably of no significance.

*Investigations.*—Urine: no abnormalities. Blood count normal. Electrolytes normal. X-rays of hands and feet show some retardation in development as judged by the ossification centres. Examination for urinary porphyrins and amino acids was negative.

Fæcal fat output over three days was also within normal limits. Examination for arsenic content of the hair was normal. Microscopical examination of the skin showed heavy tattooing of the superficial dermis by clumps of melanin-containing histiocytes. There were no inflammatory changes or increase in pigment in the epidermis.

*Comment.*—This pigmentary disturbance is probably an hereditary abnormality rather than a racial or acquired defect. The distribution of the pigmentation is quite unlike that seen in Addison's disease. In hæmochromatosis the pigmentation is uniform and is not dappled. Raindrop pigmentation might suggest arsenical poisoning but there is no sign of dyskeratosis in our case. Similar types of pigmentary anomaly have been described by Cole *et al.* (1955), by Engman (1935) and by Gordon (1940) as dyskeratosis congenita and congenital atrophy of the skin. In these cases, however, the pigmentation was of much later onset in life and was associated with defects of the skin appendages and the mucous membranes. Our case is almost identical with that described by Wende and Bauckus (1919). They described a family of 4 children, in which 2 were affected, their ages being 9 years and 13 months, and their pigmentation starting at about the age of 1 year. In the case of the elder child the pigmentation became maximal at the age of 5 and it then began to fade and was less marked by the age of 9. The pigmentation was noted to be dappled in parts, with white macules present in the pigmented area, and was similar in distribution to our case.

*Addendum.*—I have since been told of 2 similar cases in brothers, who were shown by Dr. Pegum to the Society three years ago (Pegum, 1955).

REFERENCES

COLE, H. N., RAUSCHKOLB, J., and TOOMEY, J. (1955) *Arch. Derm. Syph., Chicago*, **71**, 451.
ENGMAN, M. F., Jr. (1935) *J. Amer. med. Ass.*, **105**, 1252.
GORDON, H. W. (1940) *Brit. J. Derm.*, **52**, 258.
PEGUM, J. S. (1955) *Proc. R. Soc. Med.*, **48**, 179.
WENDE, G. W., and BAUCKUS, H. H. (1919) *J. cutan. Dis.*, **37**, 685.

**Dr. R. J. Cairns:** I am indebted to Dr. Wallace for investigating this case from the biochemical angle. I first saw the patient when she was about a year old and showing a diffuse melanosis with mottled depigmentation. Other physical signs then were blue sclerotics, a rather pinched facies and tapering

of the fingers. Since then the melanosis has increased and it has been noticed that the child is undersized for her age. Histological examination shows that the excessive pigmentation is confined to the dermis and presumably it is the result of a widespread pigmentary incontinence. Investigation directed towards detecting abnormalities of amino-acid metabolism have all proved negative.

**Dr. J. S. Pegum:** This little girl is almost identical with two brothers I showed to this Section in 1955 under the heading of "diffuse pigmentation in brothers of the Wende and Bauckus type" (*Proc.*, **48**, 179). They were also of white stock, and they were white at the time of birth and then subsequently they became dark. I have been following them and the pigmentation has been fading. I was not able to shed any light on the ætiology, but I did look up the literature at the time and Cockayne suggested that this was due to a recessive gene. The other thought we had about it was that possibly it was related to an increased secretion of the melanocyte-stimulating hormone of the pituitary. One of my patients was given moderate doses of prednisone to see whether that hastened the fading of the pigmentation; it was fading at the time and it is doubtful whether it had any effect or not.

**Onycholysis from Adhesives.**—G. C. WELLS, M.R.C.P.

Mrs. A. C., aged 32.

She noticed breaking of the finger nails during the past month. Her nails had previously been healthy. She started to use adhesive nail covers about six weeks ago. After wearing them for two weeks, a second set was applied, at which time some cracking of the nails was noticed. When, after a further fortnight, the covers were peeled off, the finger and thumb nails were found to be badly damaged.



FIG. 1.

*On examination.*—The distal two-thirds of the nail plates are whitened with partial separation from the nail beds, and the distal thirds of the nail plates are breaking away (Fig. 1).

*Comment.*—Varying degrees of nail damage have followed the use of this type of cosmetic in a considerable proportion of wearers, and I understand that these "stick-on" nail covers have been withdrawn from the market.

**Dr. C. D. Calnan:** This type of plastic nail film as a substitute for nail varnish has previously been used in the United States, and has produced the same type of dystrophy of the nails. It was withdrawn from circulation there, and has now been withdrawn from the market in this country. The nail dressings are made from a coloured cellulose or plastic film which is stuck with an adhesive mass similar to that used for medicated plasters. There is sometimes another type of adhesive in-between. There is an interesting field for study in the mechanism by which these preparations produce this severe nail damage. It may lead us to understand the nature of some idiopathic nail dystrophies.

**Dr. D. S. Wilkinson:** I had occasion to try out some similar adhesive nail covers on a number of patients. We found the same effect—though less marked—occurring in a quarter to one-third of the trials: the nails split and broke away in a similar manner. The other patients were not affected. It occurred quite typically after the second or third week, rarely before that. We tried to find out the cause and did a number of patch tests. There did not seem to be any sensitization or irritant effect from the nail covers themselves and I thought it might be due to a purely physical action. Further studies of this problem are being made.

**Dr. Brian Russell:** I have a patient with candida infection of the nail plates and I suggested to her that she put these nail covers on, to improve their appearance. She has not complained of any ill-effect but in view of what has just been said I wonder if similar coverings might prove to have some therapeutic value in candidiasis or trichophytosis of the nail plates, by causing their disintegration.

**Dr. D. S. Wilkinson:** During the trials I mentioned, a few patients who had some pre-existing dystrophy of the nails were very satisfied with the covers, and indeed keep asking for more of them. They seemed to be of some value in that very limited group, but I do not know whether these patients would run into trouble if they kept on using them for six months or more. I do not think it makes any difference how frequently the nail covers are changed; the splitting seemed to occur if they were replaced weekly.

**Calcinosis.**—E. N. M. JOHNSTON, M.R.C.P.

C. S., female, aged 8 years.

*History.*—Over the past three to four years small painless tumours have appeared in the skin and subcutaneous tissues around the left knee-joint. One similar tumour occurred on the outer side of the left elbow. Some of the lesions have been noted to increase slowly in

size: fifteen months ago three were excised but more have subsequently appeared. One of the older lesions discharged creamy white material after massage. Apart from a severe graze of the left knee four or five years ago there has been no history of trauma. Raynaud phenomena have not occurred.

*Past history.*—Mumps, measles, rubella, pertussis.

*Family history.*—Non-contributory.

*On examination.*—A fit plump child. Left elbow: A small firm oval yellow tumour attached to the skin was present at the lateral side of the antecubital fossa. Left knee: Similar tumours of various shapes and sizes could be seen or felt at different levels of the cutis and subcutis in the region of this joint. Scarring was also present. The pre-patellar bursa was swollen and hot. Full extension of the joint appeared slightly limited. Hands: The skin over the dorsal surface of interphalangeal joints showed small circumscribed red thickening with some white areas. No changes of scleroderma were present. Routine examination of other systems revealed no abnormalities.

*Investigations.*—Blood count and E.S.R. normal. Serum calcium, plasma phosphorus, alkaline and acid phosphatase, blood urea, serum cholesterol, total lipids and beta lipoproteins were all normal.

X-rays: Chest, skull, shoulders, hip-joints, long bones, and feet normal. Abdomen: No evidence of nephrocalcinosis. Forearms: On the left side there is calcification in the soft tissue of the outer aspect of the elbow. No calcification is seen on the right side. The wrists are rather unusually shaped with unusual tilting of the articular surface of the radius. No calcification is seen in the parts of the digits included in the film. Knees: Extensive patchy calcification is present around the left knee-joint.

*Comment.*—In a review of the literature of calcinosis no case of unilateral deposits in a child could be found.

**Dr. Brian Russell:** The atrophic changes on the extensor aspects of the joints suggest to me dermatomyositis. I think this may be a burned-out dermatomyositis of relatively mild intensity.

**Lichen Nitidus.**—H. T. H. WILSON, M.R.C.P.

H. T., male, aged 43. Construction engineer.

*History.*—Ten to fifteen years ago he noticed a small scaling patch in the right palm. Since then there has been a gradual extension over the palm (Fig. 1) and recently reddish patches have appeared over the 4th and 5th knuckles of the right hand. Two years ago a patch developed on the left palm.

*Past history.*—Tonsillitis on several occasions. Rubella two years ago.

*Family history.*—Irrelevant.

*On examination.*—The right palm is studded with pinhead-sized keratotic patches. The left palm is similarly but less severely affected. Over the fourth and fifth knuckles of the right hand are two small patches clinically resembling lichen nitidus. There is a similar patch on the left posterior axillary fold; buccal mucosa free. He has recently suffered a mild attack of herpes zoster.



FIG. 1.—R. palm showing lichen nitadus before treatment.



FIG. 2.—Regression following Triamcinolone

*Histology* (5.3.58).—There is a minute œdematous granuloma pushed up in a papilla consisting of round cells, endothelial cells and one or two small giant cells. The histology is that of lichen nitidus.

POSTSCRIPT.—Regression of the lesions followed Triamcinolone 4 mg. three times daily for four weeks, followed by 4 mg. twice daily for two weeks (Fig. 2).

(*To be continued in October "Proceedings".*)

# Section of Surgery

President—A. DICKSON WRIGHT, M.S., F.R.C.S.

[*March* 5, 1958]

## DISCUSSION ON HAND INJURIES

**Dr. M. Iselin** (Paris):

### "*Delayed Emergency*" *in Fresh Wounds of the Hand*

First of all I shall endeavour to explain the concept of "delayed emergency" which is applicable to all types of surgical emergency. Then I shall give the results obtained in my own hospital on fresh wounds of the hand.

In my youth an emergency meant that one operated as soon as the patient arrived in hospital. Each minute which passed was a minute lost. I have seen perforated ulcers, intestinal obstructions, empyemas, and compound fractures brought directly from the ambulance to the operating theatre. The results were bad, but were attributed to delays in calling the doctor, in making the diagnosis, or on the part of the ambulance service. With the advent of suction in intestinal obstructions and perforated ulcers, surgeons were enabled to delay in operating on such patients. Thanks to the blood, water and salt balance which it was possible to obtain, operations could now be performed on a better prepared patient.

A disadvantage was that the surgeon had to take the responsibility of deciding the best moment for the operation. The result in France was that surgeons sometimes operated too late and under worse conditions. The mistake lay in the lack of precise definition of an emergency. A new term was necessary, and I coined that of "delayed emergency", implying a state of emergency in which action was taken only when the patient was in best condition for operation.

This concept applies to surgery of the limbs. The traditional teaching was to operate within six to eight hours and, if this was not possible, to dress the wound and operate later. This had the disadvantage that operation, often long and complicated, took place on a patient without preparation, possibly a full stomach, and on a skin in uncertain condition: but surgeons preferred avoiding the danger of infection, hence surgery was done secondarily, often in conditions more serious than they had been initially.

To-day, advances in chemotherapy and antibiotics, together with improved methods of skin preparation, cancel the arguments for immediate operation. According to the hæmatocrit findings, we can prescribe any necessary correction by blood transfusion. In all cases, we give proteins parenterally, for our injured are unhappily often in a bad general condition. Operation is performed when conditions have become optimal, as judged by the state of the skin and the general condition of the patient. It is impossible to give a precise number of hours. Certain hands, for example, will require two, three, even four days before they are perfectly clean, due to the condition of the epidermis and type of injury. The general condition of some patients may also require pre-operative care for several days. For most patients, the delay does not need to be long, and operations are usually done within six to twenty hours, though we have waited as long as four days.

The application of such a plan has the great advantage of permitting at the primary operation complex procedures which under classical conditions would only be done secondarily as part of the surgery of repair, e.g. an osteo-synthesis of a fracture, a complex skin plastic repair or repair of a tendon or nerve. There is a great advantage in doing the most complete operation possible on the first occasion when patient, skin, and injuries are in the best possible state.

This routine "delayed emergency" technique has led me to revise my ideas on the immediate treatment of wounds of the flexor tendons. The present procedure is to wait for cicatrization and to operate secondarily—not by suture, but by graft according to Pulvertaft's technique. I consider, however, that the advantages of suturing are evident—a gain of time and undamaged muscular power. In case of failure, there is always the possibility of intervention either by secondary liberation of tendinous adhesions or by graft. The strong argument against the danger of immediate suture was the risk of infection but with the concept of "delayed emergency", we can suture and repair under far more favourable conditions.

## Results

Many young assistants have been slow to accept this concept, and, therefore, it is only recently that the words "delayed emergency" appear in the case histories of our own hospitals. This omission makes it very difficult to give statistics. It is, however, possible to make certain comparisons. Thus, in cases of crushed ungual phalanx, 10 were treated from six to thirty-six hours after injury, the majority within eighteen to twenty hours. Only one had an infection, which was very light and did not prevent the patient resuming his job twenty-five days after injury. Whereas out of 8 identical injuries in which removal of bone splinters and suture were done immediately, 3 became infected with forty days subsequent incapacity.

We have found in our records 6 cases of section of flexor tendons and nerves; all were operated on between twenty-six hours and four days after the injury. One was a cut at the wrist with section of the tendons and median nerve treated by direct suture; one a section at the thumb, treated by direct suture; two re-insertions and "sutures appuyées", and one "suture bloquée" (Iselin, 1958). There was no infection and only one small aseptic skin loss at the angle of a flap. The extensor tendon cases numbered 4 and were operated on after twenty to forty-eight hours. The last case was a severe road accident with all tendons severed in the hands.

There were 7 injuries requiring cover by cross-finger flaps of the base of the ungual phalanx, which I consider most important to preserve. 5 were repaired the following day, 1 on the second day, 1 after the fourth day. In 1 case the third and fourth fingers were skin-grafted, in another the *left* middle and the *right* ring fingers were affected. The results were normal, without infection, with incapacity time thirty-nine to seventy-six days. There were 4 compound fractures which were treated by "delayed emergency" of twenty to forty-eight hours. Finally in a case with injuries from a rolling-mill the loss of substance was treated by free grafts. The wounds were excised, immobilized and covered within eighteen to sixty hours after injury. The following is an illustrative case: It is that of a man who had been injured at his factory in the country. His fingers had been through the two rolls of a carding machine. The dorsal side of the hand had been skinned and half of the bones and the ungual phalanx of the middle finger were as flat as a pancake with a forward luxation. He arrived in Paris in the evening. At once his hand was cleaned, treated with penicillin, and immobilized on the standard apparatus. Two days later everything was clean, and it was possible to excise the damaged tissues, reduce the displacement of the phalanx, put it in good position with a small pin and finally cover the wound with grafts. The hand remained aseptic, and three months later the patient had such a good functional result that he could play the organ again.

By way of contrast we recently had a case of a woman who arrived in hospital with a knife wound of the commissure of the thumb received just an hour before. The wound and her hands were perfectly clean, the knife (a butcher's knife) was not particularly soiled. The intern who saw her obtained hæmostasis and performed immediate suture under antibiotic protection. Alas, the following day the hand was swollen and pus oozed from the gaping wound, the sutures having given way.

I hardly hope to have convinced you, for it is difficult to accept new ideas, even though they may appear logical, when they conflict with accepted principles. "Delayed emergency" cannot be defined by precise rules. It is rather an attitude of mind which brings with it new decisions for the surgeon who must choose the right moment for operation.

## REFERENCE

Iselin, M. (1958) Atlas du Technique en Chirurgie de la Main. Paris.

**Mr. John N. Barron** (Salisbury):

*Introduction.*—In planning the treatment of hand injuries, a number of fundamental considerations should be noted. First, the patient's occupation should be considered in all its details, as from this information the aims of treatment can often be clearly defined. Much time can be wasted in pursuing reconstructive procedures which, in the long run, are not repaid by any material benefit. Trauma to the hand is a mixture of "crush" and "cut". The greater the "crush" element the more severe will be the reaction and the complications of œdema, extravasation, and hæmatoma. Pure cutting injuries destroy a minimum amount of tissue. The prognosis will obviously be affected by these simple facts. In burns an estimate of the temperature and length of exposure are important and in electrical injuries the type of current and its voltage can be useful guiding points. The greatest problem in hand surgery is œdema. The routine use of methods for its prevention and treatment are essential if good results are to be achieved such as atraumatic surgical technique, proper drainage when necessary, high elevation and the application of cold.

*Emergency treatment.*—Many hand injuries are open and primary treatment should in most cases include wound closure. Suture under tension is not acceptable and where there is tissue loss involving the integument, some form of skin graft should be used. Free grafts are useful when skin cover only is required but the ingenious use of flaps is often called for with wounds requiring replacement of skin and subcutaneous tissue. Thenar and cross-finger flaps are often valuable and occasionally it is necessary to resort to cross-arm, chest, or abdominal flaps.

Primary tendon repair is usually justifiable in extensor tendons and also in the flexor group at the wrist or in the palm. The results of flexor tendon repair in the fingers are so variable that there are many individual preferences. In wounds caused with a minimum of "crush", i.e. where the wounding instrument is really sharp, there may be a place for primary flexor tendon repair in the fingers. The recoil effect should be assessed because flexors which are severed when under tension—as when grasping—recoil back into the palm, tearing up the synovial and vincular attachments and causing great havoc in the sheath and in the palmar space. The œdematous reaction which follows makes any attempt at primary repair hazardous. Digital nerve suture is justifiable as a primary procedure and will often give most acceptable results.

Much time can be lost by attempting to save a finger with a complex injury. Fractures or fracture dislocations with associated tendon severance seldom produce a wage-earning finger when eventually healed. An assessment of the injury taking into account the patient's occupation will often dictate amputation as the correct line of treatment. When function and power are the main considerations, amputations through the most distal feasible joint give the best results. In all cases the cartilage should be removed from the stump and the bone end slightly coned. Standard flaps are seldom possible but accurate stump cover should be fashioned from available skin. All stumps should contain full thickness subcutaneous tissue. For most manual workers the proximal phalanx of the index and fifth fingers should be preserved if possible. The hand may not look so tidy, but if there is a full range of movement in the metacarpophalangeal joint the value of the phalanx is indisputable. In women there may be an indication for the proximal oblique amputation through the second or fifth metacarpal as this produces a tidy hand, cosmetically superior to the short finger stump.

*Reconstructive surgery.*—Although there is a vast field for reconstructive endeavour in hand surgery, two points only will be discussed:

*The opposition post.*—In mutilated hands where only a functioning thumb is present, the fingers having been lost, the construction of an opposition post against which the thumb can act may well be indicated. This often requires the addition of a tubed skin graft and bone transplant to make good the tissues lost and is therefore a time-consuming programme. It can be stated that these opposition posts are of academic interest only unless they are designed to have hand skin with normal sensation on the surface to which the thumb will oppose. This feature should be seen to be quite clearly possible before the repair is started.

*Thumb replacement.*—Such is the importance of the thumb in the pattern of function of the hand that many methods have been devised for thumb replacement. Once again the occupational assessment is of great importance, as to some people the loss of a thumb may not be such a great disability. In many cases a simple phalangization of the remaining metacarpal stump may suffice, giving a perfectly adequate grip. Where the stump is very short the transplantation of the index finger into the position of the thumb by the operation of pollicization is a modern advance which should be used if the patient is seriously handicapped.

**Mr. L. W. Plewes** (Luton):

*Rehabilitation in Hand Injuries*

This brief contribution is based on opinions formed during fifteen years' experience in the field of rehabilitation. Here is our four-point programme for rehabilitation of the injured hand at the Luton and Dunstable Hospital:

(i) The ideal form of rehabilitation is normal activity.
(ii) Prevention and control of œdema.
(iii) Prompt treatment of pain.
(iv) A high target.

(i) *Normality is the ideal.*—No one can seriously dispute that normal activities re-started at an early stage will speed recovery quicker than any artificial programme: all the established conditioned reflexes, familiarity, and the soothing effect of normal surroundings are used. One way to achieve this is to alter standard treatment procedures in such a way that normal function is possible. Here are two simple examples: The recognized method of treating a rupture of the distal extensor tendon attachment in this country is by plaster fixation of the finger with the proximal interphalangeal joint flexed and the distal interphalangeal joint extended. The fact that this splintage prevents normal use is borne out by the recent report on mallet fingers from Moberg's Clinic (Bäckdahl, 1956). It was reported that 95% of patients with this injury were unable to return to work until the finger plaster had been removed six weeks later. Another method of recent origin is the fixation of the distal finger-joint in hyperextension and the proximal joint in flexion by using an intramedullary metal pin. This method, too, prevents the normal use of the hand. If, however, the distal joint only is splinted leaving the proximal joint free, the patient can and does return to almost any form of work. The result of treatment by this method in 600 cases was satisfactory, provided that the initial splinting was continued for at least six weeks and night splinting for another six weeks.

The second example is fracture of the neck of the fifth metacarpal. The secret of treatment is to disimpact the fracture and once this is done it is not necessary to double up the little finger in plaster with 90 degrees flexion at the metacarpophalangeal and proximal interphalangeal joints. Reduction is just as easily maintained by a plaster trough on the ulnar side of the hand with gentle padded pressure on the palmar surface of the head and the dorsal side of the shaft. The metacarpophalangeal joint is kept at 30 degrees flexion and the interphalangeal joints are free. A patient with this type of plaster on his hand can manage any kind of normal dry activity.

Another way of achieving normality is to ensure that operative treatment and splintage are secure enough to stand up to normal stresses and strains. For example, an apprentice blacksmith was able to return to his job, although he had plaster on both sides, for a Colles' fracture on one and a Bennett's fracture on the other.

Thus, either with modification of our method of treatment or with orthodox splinting, in 99% of hand injuries, the ideal rehabilitation, i.e. return to work within forty-eight hours, is possible and these patients never see the inside of a rehabilitation centre or a physiotherapy department, or even the inside of a solicitor's office.

Two points are worth mentioning in this treatment:

(*a*) The hand that is working normally gets moist with perspiration and if covered with many layers of wool and bandage, the skin becomes soggy and unhealthy. If it is stressed that such dressings are only an encumbrance after the third day, in most cases hands will remain supple and strong, instead of stiffening with inactivity.

(*b*) The surgeon must be prepared to persuade both employer and employee of the advantages to both parties of the treatment offered. This leaves only 1% of all hand injuries that require a special programme. Most of these patients will be in hospital at first. In these cases two factors require consideration—infection and œdema.

A great deal has been accomplished in recent years in the prevention and treatment of infection in compound injuries, but I should here like to stress the importance of the prevention of œdema.

(ii) *Œdema destroys function.*—Œdema which persists can fix the small joints of the hand as effectively as any arthrodesis. Fibrin from the abnormal tissue fluid is deposited in the capsule and soft tissues, is replaced by scar tissue and the joint may become ankylosed. The prevention of œdema is the most important point in the successful rehabilitation of the severely injured hand and during the first day positive steps must be taken to control the inevitable onset of swelling. The first step is operative treatment, and this should be followed immediately by elevation and cooling. As soon as all signs of active inflammation are over the patient is admitted to the rehabilitation centre—perhaps only for a couple of hours on the first day—a full day as soon as possible. Surgeon, patient and rehabilitation team should realize that this business of getting a hand well again is a full-time job. How are we

going to persuade a patient to use his damaged hand for many hours a day at this early stage when he knows in his own mind that it will tire after a few minutes exercise? We give him a job that rapidly becomes automatic, i.e. we make use of a conditioned reflex. The patient is seated on a low stool and is required to operate a simple single-spindle drilling machine. The operating handle is deliberately set at a high level so that the injured hand is working above shoulder height. It takes only a few minutes to master the machine and then the hand activity becomes automatic, the person's attention being focused on the metal object to be processed.

The principle is function in elevation and a day's work. These are the essentials, but the refinements are helpful. The cold blue hand works better when it is warm. This is quite simply arranged by having a supply of warm air to a Perspex box surrounding the hand. Gadgets to encourage or guide the thumb and fingers through certain movements are helpful though not essential but of equal importance is the fact that this is the surest way of winning the interest of the engineer. I think it is essential, if one is going to use simple industrial methods in rehabilitation, to ask for complicated gadgets once in a while to make rehabilitation compare with surgery at its best and industry at its most interesting.

We had a patient in the centre who had cut most of the structures in front of his wrist. When his opponens pollicis showed some slight but definite action the workshop staff were asked to produce a gadget that could be fastened to the handle of a drilling machine and would guide the thumb into opposition each time the lever was pulled down. The man who produced this equipment, which proved successful, went on to improve it and eventually turned out a beautiful mechanical toy. He was a skilled instrument maker and was admitted to the rehabilitation centre to get used to factory life after being off work for several years with an anxiety neurosis. This job, which took him many weeks to do, helped his mental recovery in no small way. I thought the whole idea was a good example of applied psychology by the rehabilitation superintendent. Patients who employ their skill to help others get well help themselves in the process.

The surgeon has his part to play in this stage of the programme because the nature of the initial injury and the quality of the immediate surgery will probably decide whether successful rehabilitation is possible. To be sure of success the surgeon must watch the recovery programme closely and he cannot expect the best if he delegates this to a junior or to a colleague in another specialty. He must be ready to cope with pain which brings us to the third main point.

(iii) *Pain destroys function.*—Pain is a most important factor interfering with the function of the hand. Let us take for example the swollen, painful, functionless hand of Sudeck's atrophy. In the early stages pain is controlled by certain physical methods and analgesics, but the secret of recovery is function in elevation. The power of grip is charted daily. An attack of pain causes a sudden and dramatic fall in power. The pain is localized and a trigger area found and injected with a local analgesic. This is followed by a return of power and function. If this episode of pain were not terminated by prompt action success would not have been possible. These charts of daily grip power are interesting and instructive and encourage both patient and staff to keep an enthusiastic outlook on the road to recovery. We are also charting the hand volume each day and collecting an increasing amount of interesting information about the behaviour of these swollen hands. There is no doubt that function in elevation results in a measurable diminution in hand volume in one hour.

(iv) *Set the target high.*—At the beginning of each programme one must have a target which should be high, but not impossibly so. It could be based on the average time off work for relatively standard injuries, when other factors are ideal. For instance, our target for return to work whether normal, modified, or selected is for patients with:

Colles' fracture—two and a half days.

Scaphoid fracture—one and a half days. This is a shorter target than for a Colles' fracture because the wrist in this case is not so painful and because the thumb need not be included in plaster unless there is displacement of fragments.

Bennett's fracture—eight days. A longer period because operative treatment is always necessary, but after operation the function of the hand can be near normal because it is not necessary to include the metacarpophalangeal joint in plaster.

Complicated injuries, of course, require more thought and often negotiation with employers. Sometimes, the patient can be supplied with special lively splints to help the disabled hand to behave like normal, e.g. in extensor palsy. Stiff fingers can be encouraged to keep full passive movements by finger stalls and twin thimbles.

## REFERENCE

BÄCKDAHL, M. (1956) *Acta chir. scand.*, **111**, 151.

## BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

**Admiralty.** Notes on atomic energy for medical officers. 2nd ed. pp. 174. London: H.M.S.O. 6s. 1957.

**Agüero (O.).** Anomalías morfológicas de la placenta y su significado clínico. pp. 107. Caracas: Artegrafia. 1957.

**Alston (J. M.),** and **Broom (J. C.).** Leptospirosis in man and animals. pp. 367. Edinburgh and London: Livingstone. 40s. 1958.

**Association for Research in Nervous and Mental Diseases.** The brain and human behavior. (Proceedings, Vol. 36.) pp. 564. Baltimore: Williams and Wilkins. 1958.

**Bauer (K. H.),** ed. Die deutschen Chirurgenkongresse seit der 50. Tagung. pp. 140. Berlin, etc.: Springer. 1958.

**Beck (K. F. A.).** Missbildungen und Atombombenversuche. pp. 63. Ulm: Donau, Haug. DM. 4.20. 1958.

**Bishop (W. J.),** ed. Bibliography of international medical congresses. Prepared under the auspices of the C.I.O.M.S. pp. 238. Oxford: Blackwell. 25s. 1958.

**Bologna. Istituto Elioterapico Codivilla-Putti e Villa Blu.** Rendiconto clinico, 1950–54. Cortina. 1954.

**Castiglioni (A.).** Storia della medicina. 2nd ed. pp. 825. Milan: Mondadori. 1936.

**Crook (F.).** Integration of science. pp. 99. Lausanne: Ère Nouvelle. 1958.

**Deichmann (W. B.),** and **Gerarde (H. W.).** Signs, symptoms and treatment of certain acute intoxications. 2nd ed. pp. 154. Springfield, Ill: C. C. Thomas. 27s. 6d. 1958.

**Dejean (C.),** ***et al.*** L'embryologie de l'oeil et sa tératologie. pp. 728. Paris: Masson. 1958.

**Gordon-Taylor (Sir Gordon),** and **Walls (E. W.).** Sir Charles Bell: his life and times. pp. 288. Edinburgh and London: Livingstone. 42s. 1958.

**Gutierrez Rivas (E.).** Dr. Harald Seidelin: su obra en Yucatan y algunas de sus actividades científicas en otros lugares. pp. 285. Yucatan: Merida. 1951.

**National Association for the Prevention of Tuberculosis.** Carcinoma of the lung—a N.A.P.T. symposium. pp. 48. London: N.A.P.T. 6s. 1958.

**National Association for the Prevention of Tuberculosis.** Cardiac problems for chest physicians—a N.A.P.T. symposium. pp. 39. London: N.A.P.T. 5s. 1958.

**Palmer (H. A.).** Abreactive treatments and general practice. (Reprinted from the *Medical Press*, Jan. 22, 1958.)

**Penfield (W. G.).** The excitable cortex in conscious man. (The Sherrington Lectures. 5. University of Liverpool.) pp. 42. Liverpool: University Press. 10s. 6d. 1958.

**Shanks (S. Cochrane),** ***et al.*** A textbook of X-ray diagnosis by British authors. Vol. 3: Abdomen. 3rd ed. pp. 883. London: Lewis. £6. 1958.

**Sokół (S.).** Historia Gdańskiego Cechu Chirurgów 1454–1820. pp. 270. Wrocław. 1957.

**Sorsby (A.),** ed. Systemic ophthalmology. 2nd ed. pp. 682. London: Butterworth. £5 5s. 1958.

**Toverud (G.).** The influence of war and postwar conditions on the teeth of Norwegian school children. pp. 235. New York: Milbank Mem. Fund. 1957.

**United States. Veterans' Bureau. Department of Medicine and Surgery.** Medical research in the Veterans' Administration. pp. 1386. Washington: Govt. Printing Office. 1958.

**Watkins (A. L.).** A manual of electrotherapy. pp. 259. Philadelphia: Lea and Febiger. 37s. 6d. 1958.

**Yudkin (J.).** This slimming business. pp. 191. London: MacGibbon and Kee. 195[illegible].

# Section of Endocrinology

President—C. N. ARMSTRONG, M.D., F.R.C.P.

[*April* 23, 1958]

**Crohn's Disease with Features Suggesting Addison's Disease.**—D. MATTINGLY, M.B., M.R.C.P. (for Professor F. T. G. PRUNTY, M.D., F.R.C.P.).

Mrs. C. E., a housewife aged 38, was admitted to hospital in April 1957, complaining of progressive loss of weight, lassitude, increasing facial pigmentation and bouts of mid-abdominal pain associated with watery diarrhœa for seven months.

She was thin and had early clubbing of her fingers. There was pigmentation of her face, neck, upper limbs, buccal mucosa and lips. Her blood pressure was 115/60. She had a normal white cell count, a hæmoglobin level of 83% and an E.S.R. of 52 mm. in one hour (Westergren). Plasma sodium was 138 mEq./l., plasma potassium 4·4 mEq./l., plasma chlorides 110 mEq./l., and plasma $CO_2$ 27 mEq./l. The blood urea was 20 mg.%. She excreted 80% of an oral water load in four hours. During four days of intramuscular ACTH gel urinary 17-ketogenic steroids rose from an average of 5·4 mg. per twenty-four hours to 57 mg. on the fourth day (Table I). This response was thought to exclude Addison's disease. A

TABLE I.—RESULTS OF ACTH TEST

| | Control period | | | ACTH gel. 20 units b.d. | | | |
|---|---|---|---|---|---|---|---|
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 17-ketosteroids mg./day | 7·9 | 8·5 | 9·2 | 10·9 | 12·3 | 11·3 | 14·6 |
| 17-ketogenic steroids mg./day | 4·7 | 0·9 | 6·2 | 20·5 | 46 | 49 | 57 |
| Weight in lb. | | | | 117 | 118 | 119 | 122 |

glucose tolerance test and vitamin A absorption test were normal. On a diet containing approximately 60 grams of fat a day she excreted a daily average of 5·6 grams fæcal fat over a collection period of six days. This suggested that mild steatorrhœa was present. A chest X-ray was normal. A barium meal and follow-through and a barium enema showed changes in the terminal ileum consistent with regional ileitis (Fig. 1). Examination of her stools was negative for tubercle bacilli, dysentery organisms, cysts and amœbæ.



FIG. 1.—Small bowel meal showing last few feet of the ileum. The calibre is irregular and the mucosal pattern abnormal, in places coarse and in others absent. The appearances are consistent with regional ileitis.

She was put on a low residue diet and oral cortisone. Symptomatically she improved and put on 30 lb. in weight. She has been maintained in reasonable health now for a year but reduction of the dose from 100 to 62·5 mg. a day has led to a return of her abdominal pain and diarrhœa. A mild anæmia persists despite a course of intramuscular iron, and occasional frank blood appears in her stools.

*Comment.*—The combination of loss of weight, lassitude, gastro-intestinal upset and increasing pigmentation suggested Addison's disease but this was ruled out by the normal response to ACTH (Mencer Martin *et al.*, 1957). Using the same batch of ACTH in the same dosage it was found that the mean highest daily excretion of 17-ketogenic steroids was 68·7 mg. (standard error 6·9) in a group of female patients without evidence of adrenal dysfunction.

Although Addisonian-like pigmentation is not uncommon in association with steatorrhœa, Cooke (1955) described pigmentation in only 5 out of his series of 90 patients with regional ileitis. Clubbing, however, was present in 48. Crohn (1949) makes no mention of abnormal pigmentation in his series of 298 cases and clubbing was only present in 17, the incidence being highest in the patients with diffuse ileo-jejunitis. Both features are, therefore, consistent with the radiological diagnosis though the increased pigmentation is apparently rare.

This patient was treated with oral cortisone in view of the encouraging reports on the use of gluco-corticoids in this disease in the absence of any urgent indication for surgery (Crohn, 1958). Despite the marked symptomatic improvement the disease is still active, judging by the return of symptoms on reduction of the dose, the anæmia and the presence of blood in the stools.

REFERENCES

COOKE, W. T. (1955) *Ann. R. Coll. Surg. Engl.*, **17**, 137.

CROHN, B. B. (1949) Regional Ileitis. London.

—— (1958) *Gastroenterology*, **34**, 300.

MARTIN, M. M., GRAY, C. H., LIVINGSTONE, J. L., and LUNNON, B. J. (1957) *J. clin. Endocrin.*, **17**, 1168.

**Conn's Syndrome.**—P. K. M. BARRETT, M.B., R. I. S. BAYLISS, M.D., F.R.C.P., and J. R. REES, M.B., M.R.C.P.

Miss W. M., aged 47.

*History.*—Recurrent urinary infection aged 20 and 33. Thereafter well until 1955 when increasing lethargy and nocturnal frequency of micturition commenced. In September 1955 she developed severe weakness, particularly of the legs, and was admitted to a fever hospital as a suspected case of poliomyelitis. Examination showed photophobia, tenderness and paralysis of lower limbs and absent reflexes. Blood pressure 180/100 mm.Hg. The diagnosis was not confirmed and she recovered spontaneously after six weeks. Subsequently she remained weak and a further severe attack of paralysis was precipitated by broncho-pneumonia in May 1957 when her serum potassium was 2·6 mEq./l. Blood pressure 150/90 mm.Hg. She responded well to potassium supplements (*circa* 130 mEq. potassium daily) and was also found to have pernicious anæmia (Hb 31 grams%) which was treated with vitamin $B_{12}$.

She then developed a series of neurological incidents commencing with a right hemiparesis in December 1957 from which she made a good recovery. In January 1958 she had a short illness with confusion and signs of meningitis but no evidence of infection in the C.S.F.

In February 1958 her confusion recurred with severe dysphasia followed by a right-sided Jacksonian convulsion, again with good recovery. These episodes were thought to be due to cerebral atherosclerosis associated with hypertension, and left carotid arteriography showed irregular tortuous cerebral arteries.

*Examination.*—General condition good on potassium supplement. No weakness. Mild generalized pigmentation. Slight residual dysphasia. Slight cardiac enlargement. Blood pressure labile, average 175/105 mm.Hg (130/90 to 220/160).

*Investigations.*—Serum electrolytes: Serum potassium 2·5–2·8 mEq./l., rising to normal levels on supplements. Serum sodium 145, chloride 106, alkali reserve 28 mEq./l. Serum calcium 10·3, phosphate 4·3 mg.%. Blood urea 14–35 mg.%. Serum magnesium 1·9 mg.% (Dr. Ian McIntyre).

Chest X-ray: Slight cardiac enlargement.

ECG: Changes of hypokalæmia.

Urinalysis: Slight albuminuria; occasional hyaline and granular casts. Numerous C.S.U.s sterile except in May 1957 when *E. coli* was grown.

Renal function tests: Urine concentration (twelve hours) sp. gr. 1020. Urine concentration after 5 units pitressin tannate in oil sp. gr. 1019. Urine dilution sp. gr. 1000. 70% standard water load excreted in four hours. Urinary pH after 5 grams ammonium chloride: pH fell to 6·8 pre-op.; pH fell to 5·9 post-op.

Urea clearance test: 66% average normal.
I.V.P. normal.
Renal biopsy: mild tubular vacuolation, otherwise normal.
Presacral pneumogram: normal suprarenal outlines.
Urinary aldosterone: (Prof. F. T. G. Prunty.)
With potassium supplement 6·7 μg./24 hours.
Without potassium supplement 1·8 μg./24 hours.
Post-operative 0·3 μg./24 hours.
(Normal range 3–7 μg./24 hours.)
Glucose tolerance test: Normal.
Fæcal fat excretion: Mean of five days—5·7 grams/24 hours.
Sodium/potassium ratios: Saliva—Pre-op. 0·9 at a flow rate of 0·8 ml./min., 1·6 at a flow rate of 3·4 ml./min.; post-op. 2·3 at a flow rate of 2·9 ml./min. Fæces—Pre-op. 0·5, post-op. 0·6.

Potassium excretion: During balance, with progressive potassium depletion, renal potassium loss averaged 54 mEq. daily with a serum potassium level of 2·8 mEq./l. (Normal excretion under these conditions less than 15 mEq. potassium daily.)

Balance data: On a high potassium intake (224 mEq. daily) a positive potassium balance of about 820 mEq. was achieved over fourteen days. An initial negative sodium balance of about 180 mEq. by the fifth day was reversed by the end of the period. On a low potassium intake (47 mEq. daily) a negative potassium balance of 88 mEq. and a positive sodium balance of 350 mEq. occurred over five days. A further balance was started on the twelfth post-operative day. Over the next five days 70 mEq. of potassium were retained and 185 mEq. of sodium were lost.

Response to low sodium diet: On a diet containing 22 mEq. sodium daily, marked sodium retention occurred with an average sodium excretion of 12 mEq. daily over seven days (range 2–19 mEq. daily).

*Operation* 14.3.58 (Mr. Robert Cox).—Postero-lateral approach. Examination of both adrenals was planned but the left was inspected first and was found to be enlarged. On removal and transection the gland was largely replaced by a round encapsulated tumour (Fig. 1). The right suprarenal was not examined. Post-operative course uneventful.



FIG. 1.—Benign adenoma occupying upper pole left adrenal. It is well encapsulated and had the typical orange colour of aldosterone-producing tumours.

*Histology of tumour.*—Benign cortical adenoma. The cells are polyhedral with rather vacuolated cytoplasm and well-defined nuclei. They appear to be derived predominantly from the zona fasciculata. No atrophy of cortical zones is seen in the adrenal remnant.

*Post-operative course.*—She subsequently remained well on a normal diet. The blood pressure fell to 140/90, but rose later to 150/110. The ECG became normal. The serum potassium rose to 5·6 mEq./l. on the fourth post-operative day and thereafter fluctuated between 4·1 and 4·5 mEq./l. Urinary acidification improved promptly but the impaired renal concentrating power remained unaffected.

*Comment.*—This patient with Conn's syndrome had a typical adrenal adenoma and responded in the usual way to its removal. Because of the unusual features, the distinction between potassium-losing nephritis and Conn's syndrome could not be made before operation. The absence of pyelonephritis in the renal biopsy, the balance data, and the response to a

low sodium intake favoured Conn's syndrome. The absence of alkalosis and hypernatræmia, the normal sodium/potassium ratios and the failure to demonstrate increased urinary aldosterone excretion were, however, unusual. Furthermore, no tumour could be demonstrated on the pneumogram, and the history of previous urinary infection with a positive urinary culture, favoured potassium-losing nephritis. This case illustrates that the diagnostic criteria in Conn's syndrome may be fallible, especially if negative, and that diagnosis may depend on adrenal exploration.

**Dr. R. I. S. Bayliss** pointed out that this case exemplified very well the difficulties in distinguishing between primary hyperaldosteronism and potassium-losing nephritis. Pre-operatively the investigatory data and the history were equally in favour of both conditions, although the normal renal biopsy favoured primary aldosteronism. The only certain way of being sure of the diagnosis seemed to be exploration of the adrenal glands.

**Cœliac Dwarfism, with Anæmia and Osteomalacia.**—O. GARROD, M.D.

Miss B., 59, saleswoman.

*History.*—Always small and underweight for her age. Lifelong tendency to occasional flatulent dyspepsia and diarrhœa. Menses began at 18, and remained regular but scanty until menopause at 40. Recurrent anæmia since at least 1940. Her disabilities have not been severe enough to interfere with her work.

*Past history.*—Osteotomy of left femur at 17 for genu valgum. Gastric ulcer diagnosed in 1944, during investigation of anæmia, and treated medically.

*Family history.*—Numerous relatives, all of normal height and health.



FIG. 1.—Patient Miss B.

*On examination* (March 1958).—A dwarf of normal skeletal proportions except for slight bowing of legs. Height 4 ft. 3 in., weight 64 lb. Pallor of mucous membranes. Skin healthy, but generalized increase in pigmentation. Scanty axillary and normal pubic hair. Breasts poorly developed. Abdomen distended with gas. Blood pressure 140/80. Urinalysis negative.

*Investigations.*—Blood: Hæmoglobin 57%; M.C.V. 71 cu. μ; M.C.H.C. 25·4%. Film shows hypochromasia, anisocytosis and poikilocytosis. Serum inorganic phosphorus 2·3, calcium 5·5 mg.%. Serum proteins 7·4, albumin 3·4, globulin 4·0 grams %.

Fæces: Pale, bulky, no tryptic activity.

Duodenal juice: Tryptic activity, 1 in 64 dilution.

Fat balance (on 50 grams fat/day): 63% absorption.

Plain X-ray abdomen: Numerous coils of dilated gut with fluid levels.

Barium meal X-rays: Stomach and duodenum normal. Jejunal mucosal pattern abnormal. Dilated ascending colon.

Skeletal X-rays: Whole skeleton shows osteoporosis, with thin cortices and coarse trabeculation most marked near epiphyses. Lumbar vertebræ show bi-concave deformity, without collapse. Pelvis shows moderate trifoliation. No Looser's zones. Minimal periosteal reaction with spicule formation in terminal and middle phalanges of fingers compatible with secondary hyperparathyroidism.

*Treatment.*—(1) High protein, low fat diet. (2) Ferrous sulphate, 180 mg. t.i.d. (3) Calciferol, 200,000 i.u./day for ten days.

*Progress.*—After twelve days of treatment, serum calcium had risen to 11·2 mg.%, and inorganic phosphorus to 3·6 mg.%. Calciferol was then stopped. Six weeks later serum calcium was 10·5 mg.%, and phosphorus 3·5 mg.%.

There has been no further diarrhœa, and the hæmoglobin has slowly risen to 72%.

*Comment.*—An unusually severe case of cœliac dwarfism (cf. Frazer, 1956) undiagnosed until presenting at the age of 59. Other features are delayed puberty, iron deficiency anæmia, and osteomalacia due to malabsorption, with radiological evidence of secondary hyperparathyroidism.

REFERENCE

FRAZER, A. C. (1956) *Proc. R. Soc. Med.*, **49**, 1009.

**Dr. D. Marrack** said that abnormal ascorbic acid saturation tests might be seen in a variety of disturbances of absorption and the abnormality was not specific for any special variety. He had seen it in malabsorption following partial gastrectomies and after surgical shortening of the small intestine, as well as in idiopathic steatorrhœa. One case did not have excessive twenty-four-hour fæcal fat in spite of failure to saturate with 1 gram of ascorbic acid daily at the same time.

**Female Pseudohermaphroditism.**—H. K. IBBERTSON, M.R.C.P., M.R.A.C.P., and RUSSELL FRASER, M.D., F.R.C.P.

Miss H., aged 22. Genital abnormality with enlarged clitoris was noticed at birth by midwife. The sex of the child was questioned at that time. Reared as a girl and developed normal female interests. She was taller than her playmates of the same age until the age of 11 years when growth ceased. An abnormal growth of pubic hair was first noticed at the age of 6 years. Hair soon appeared on the trunk and beard area, and by the age of 16 years when she left school, she required to shave daily to conceal the hirsutism. Despite these



FIG. 1.—Patient C. H. The muscular development and marked hirsutism are well shown.

changes, there was no breast development, and menstruation failed to occur. The patient was acutely aware of these abnormalities and regarded herself as a freak, and there were many episodes of depression. The parents, wishing to spare her the embarrassment of out-

low sodium intake favoured Conn's syndrome. The absence of alkalosis and hypernatræmia, the normal sodium/potassium ratios and the failure to demonstrate increased urinary aldosterone excretion were, however, unusual. Furthermore, no tumour could be demonstrated on the pneumogram, and the history of previous urinary infection with a positive urinary culture, favoured potassium-losing nephritis. This case illustrates that the diagnostic criteria in Conn's syndrome may be fallible, especially if negative, and that diagnosis may depend on adrenal exploration.

**Dr. R. I. S. Bayliss** pointed out that this case exemplified very well the difficulties in distinguishing between primary hyperaldosteronism and potassium-losing nephritis. Pre-operatively the investigatory data and the history were equally in favour of both conditions, although the normal renal biopsy favoured primary aldosteronism. The only certain way of being sure of the diagnosis seemed to be exploration of the adrenal glands.

**Cœliac Dwarfism, with Anæmia and Osteomalacia.**—O. GARROD, M.D.

Miss B., 59, saleswoman.

*History.*—Always small and underweight for her age. Lifelong tendency to occasional flatulent dyspepsia and diarrhœa. Menses began at 18, and remained regular but scanty until menopause at 40. Recurrent anæmia since at least 1940. Her disabilities have not been severe enough to interfere with her work.

*Past history.*—Osteotomy of left femur at 17 for genu valgum. Gastric ulcer diagnosed in 1944, during investigation of anæmia, and treated medically.

*Family history.*—Numerous relatives, all of normal height and health.



FIG. 1.—Patient Miss B.

*On examination* (March 1958).—A dwarf of normal skeletal proportions except for slight bowing of legs. Height 4 ft. 3 in., weight 64 lb. Pallor of mucous membranes. Skin healthy, but generalized increase in pigmentation. Scanty axillary and normal pubic hair. Breasts poorly developed. Abdomen distended with gas. Blood pressure 140/80. Urinalysis negative.

*Investigations.*—Blood: Hæmoglobin 57%; M.C.V. 71 cu. μ; M.C.H.C. 25·4%. Film shows hypochromasia, anisocytosis and poikilocytosis. Serum inorganic phosphorus 2·3, calcium 5·5 mg.%. Serum proteins 7·4, albumin 3·4, globulin 4·0 grams %.

Fæces: Pale, bulky, no tryptic activity.

Duodenal juice: Tryptic activity, 1 in 64 dilution.

Fat balance (on 50 grams fat/day): 63% absorption.

Plain X-ray abdomen: Numerous coils of dilated gut with fluid levels.

Barium meal X-rays: Stomach and duodenum normal. Jejunal mucosal pattern abnormal. Dilated ascending colon.

Skeletal X-rays: Whole skeleton shows osteoporosis, with thin cortices and coarse trabeculation most marked near epiphyses. Lumbar vertebræ show bi-concave deformity, without collapse. Pelvis shows moderate trifoliation. No Looser's zones. Minimal periosteal reaction with spicule formation in terminal and middle phalanges of fingers compatible with secondary hyperparathyroidism.

*Treatment.*—(1) High protein, low fat diet. (2) Ferrous sulphate, 180 mg. t.i.d. (3) Calciferol, 200,000 i.u./day for ten days.

*Progress.*—After twelve days of treatment, serum calcium had risen to 11·2 mg.%, and inorganic phosphorus to 3·6 mg.%. Calciferol was then stopped. Six weeks later serum calcium was 10·5 mg.%, and phosphorus 3·5 mg.%.

There has been no further diarrhœa, and the hæmoglobin has slowly risen to 72%.

*Comment.*—An unusually severe case of cœliac dwarfism (cf. Frazer, 1956) undiagnosed until presenting at the age of 59. Other features are delayed puberty, iron deficiency anæmia, and osteomalacia due to malabsorption, with radiological evidence of secondary hyperparathyroidism.

REFERENCE

FRAZER, A. C. (1956) *Proc. R. Soc. Med.*, **49**, 1009.

**Dr. D. Marrack** said that abnormal ascorbic acid saturation tests might be seen in a variety of disturbances of absorption and the abnormality was not specific for any special variety. He had seen it in malabsorption following partial gastrectomies and after surgical shortening of the small intestine, as well as in idiopathic steatorrhœa. One case did not have excessive twenty-four-hour fæcal fat in spite of failure to saturate with 1 gram of ascorbic acid daily at the same time.

**Female Pseudohermaphroditism.**—H. K. IBBERTSON, M.R.C.P., M.R.A.C.P., and RUSSELL FRASER, M.D., F.R.C.P.

Miss H., aged 22. Genital abnormality with enlarged clitoris was noticed at birth by midwife. The sex of the child was questioned at that time. Reared as a girl and developed normal female interests. She was taller than her playmates of the same age until the age of 11 years when growth ceased. An abnormal growth of pubic hair was first noticed at the age of 6 years. Hair soon appeared on the trunk and beard area, and by the age of 16 years when she left school, she required to shave daily to conceal the hirsutism. Despite these



FIG. 1.—Patient C. H. The muscular development and marked hirsutism are well shown.

changes, there was no breast development, and menstruation failed to occur. The patient was acutely aware of these abnormalities and regarded herself as a freak, and there were many episodes of depression. The parents, wishing to spare her the embarrassment of out-

side contact, encouraged her to stay at home rather than seek outside employment. At the age of 18 years, frontal baldness appeared and progressed rapidly. This was the final straw and the patient withdrew more and more into herself, refusing to discuss her obvious difficulties with her parents. She consented to specialist investigation only after six months' heart-searching and indecision.

*Examination.*—Examination revealed a stocky muscular girl with frontal baldness and marked hirsutism of beard area and trunk. Breast development was absent. The laryngeal cartilage was of male type but the voice was normal. There was genital abnormality with enlarged clitoris, a common urogenital sinus, narrow short vagina and small uterus. She was shy, blushed easily, but after initial hesitation discussed her problems freely.

*Investigations.*—Urine 17-ketosteroids 280, 253 mg./24 hours. 17-ketogenic steroids 163, 202 mg./24 hours. Pregnanetriol (Dr. Margaret Stern) 31 and 96 mg./24 hours. Plasma hydrocortisone 1·7 μg./100 ml. Presacral $CO_2$ insufflation showed bilateral adrenal enlargement. Bone X-rays showed normal development with closed epiphyses.

*Progress.*—A course of 9α-fluorohydrocortisone 10 mg. daily caused a fall of abnormal urine steroids to normal levels within five days. Ankle œdema appeared with this dosage. Treatment was subsequently continued with a combination of this drug and prednisone in varying doses as shown:

| Therapy/24 hours | Urine Steroids (mg./24 hours) | | |
|---|---|---|---|
| | 17 KS | 17 KGS | Pregnanetriol |
| Nil | 280 | 163 | 31 |
| | 253 | 202 | 96 |
| 9α F.H.C. 10 mg. | 14 | 8 | 0·8 |
| | 10 | 7 | 0·7 |
| 9α F.H.C. 2 mg. | 16 | 12 | — |
| Prednisone 15 mg. | 13 | 11 | |
| 9α F.H.C. 3 mg. | 26 | 23 | |
| Prednisone 15 mg. | 23 | 22 | — |
| 9α F.H.C. 6 mg. | 5 | 8 | 1·3 |
| Prednisone 15 mg. | 5 | 9 | 1·2 |

The patient was discharged from hospital on 9α-fluorohydrocortisone 6 mg. and prednisone 15 mg. daily. This dosage produced biochemical evidence of potassium deficiency with moderate hypertension. Satisfactory adrenal suppression was obtained, however, and a menstrual bleed occurred two months after the institution of therapy.

Future treatment will include inpatient psychiatric supervision with a view to helping social readjustment giving vocational guidance.

**Professor F. T. G. Prunty** pointed out that the pregnanetriol present would be included in the estimate of 17-ketogenic steroids. The discrepancy between the amounts of pregnanetriol and 17-ketogenic steroids was, however, so large as to indicate that there must be an excess of corticoid metabolites also in the urine. The nature of these would be of interest, but the data presented appeared to indicate that any block in corticoid syntheses could only be of partial degree, and it was strange the suppression of corticotropin secretion was apparently poor. The desirability of the continued use of 9α-fluorohydrocortisone, with its effects on potassium, as a suppressive agent was questioned.

[*May* 28, 1958]

A DISCUSSION was held on Complications of Long-term Steroid Therapy. The opening papers were as follows:

**The Response to Surgery.**—Dr. OSWALD SAVAGE.

**Post-operative Collapse and Septicæmia in Patients under Corticosteroid Therapy.**—Mr. G. SLANEY.

**Vascular Lesions in Patients on Long-term Cortisone Treatment.**—Professor E. G. L. BYWATERS.

# Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

[*March* 12, 1958]

SAMUEL HYDE MEMORIAL LECTURE
[Number 12]

## On the Fringes of Electrodiagnosis

By P. BAUWENS, M.R.C.P.
*London*

IN this lecture my point of departure must be a definition of the operative word in the title "electrodiagnosis". To me this means the application of electrology to the study of deviations from the normal behaviour of the motor unit and their interpretation to diagnostic ends. In this context motor units must be regarded as individuals in societies which, anatomically speaking, go to make up the anterior horns in the cord or the nuclei in the brain, the nerves and the muscles. Nor should their behaviour, normal or abnormal, be considered except in the light of this membership and of their share in the activities of this society. Again, the word "behaviour" of the motor unit is here intended to include not only the manner in which it conducts itself at rest and on volition, but its mode of responding to stimuli, either reflex or artificial, or to the action of certain drugs.

By and large when we speak of a clinical examination we imply that observations are made by the direct use of four of our senses—sight, hearing, touch and smell. Some might hold a brief for the imponderable sixth sense. Because of the limitation of our senses, some investigations require complex equipment, frequently demanding specialized knowledge and training. Yet in every case the intricate instrumentation is merely a convenience calculated to extend the range of our perception. As with specialized investigations in other fields, electrodiagnosis is a complementary one—generally to a neurological examination from which it varies only in the difference in approach to a more restricted problem. An electrical stimulator and an electric probe replace the patellar hammer and pairs of searching eyes, ears and hands.

For many, the intricacies of the electrodiagnostic equipment have a fascination which acts as an impediment to the appreciation of what it aims at and accomplishes. For this reason, I shall ask you to forget the complex machinery and indulge with me in a little imaginary adventure which I might well have entitled "20,000 Microns Below the Skin".

As a prelude to these mental exercises I shall ask you to imagine that your body shrinks to the point of being capable of being enclosed in a microscopic capsule, itself embedded in the muscle to be examined. From this vantage point, the workings of the muscle could be observed at first hand.

At rest the normal muscle would be a silent world. During volitional activity there would first occur an electrical disturbance produced by the propagated action potentials of the various muscle fibres composing the nearest active motor unit. If all these potentials started at the same time from their individual motor end plates towards you, provided their velocities were the same, they would summate and approach you as a sort of electrical tidal wave. After this had died down there would follow the mechanical manifestations related to the actual muscular contraction. Should your host suffer with some condition which causes the muscle fibres in the motor unit to be excited in a staggered fashion instead of simultaneously, then a series of small electrical waves would replace the large tidal wave.

As an encapsulated observer in a muscle you might well make some interesting observations and deductions in respect of the temporal dispersion of the action potentials propagated along the muscle fibre of a motor unit. Some of you will here object that by no extension of your senses would you be able to detect these electrical disturbances. This, of course, would be wrong. Electricity does affect us although we cannot lay claim to having been provided with special sense organs for this purpose, and if for electromyographic examinations we prefer to display amplified action potentials on the screen of a cathode ray tube or from a loudspeaker rather than in the shape of electric shocks, it is only because it is more comfortable, more dignified and scientifically more acceptable to do so.



FIG. 1. J. Dewe

There is something to be learned from Fig. 1 which is of importance. It will be noted that the unfortunate gentleman has just suffered a severe shock in his left leg through the unwelcome attention of a compact shoal of electric eels. Little does he realize that he is about to undergo a similar, but less unpleasant experience in his right leg, for a second shoal in a less tight formation is approaching that. The fact that the fishes are scattered means that at the most he will endure a series of minor shocks spread over a longer period. It is interesting to note that while the first shock will not be substantially affected by the position of the leg in the shoal, in the case of the second shock the pattern of the sensation will be affected by the position of the right leg in the midst of the shoal. Similarly, a change in the location of your exploratory capsule would substantially modify the pattern of the electrical disturbance only when the action potentials are staggered.

During volitional activity of a normal muscle you would come under the influence not only of the nearest active motor unit, but also that of more remote ones, and would thus be

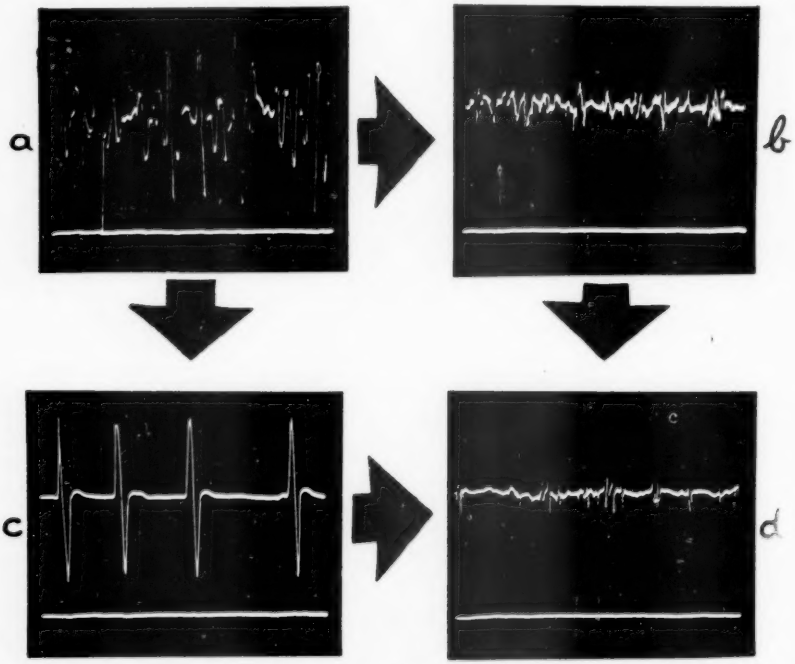



FIG. 2.—Shows the modifications that would result in the EMG tracing of a muscle (A, normal pattern) if a large proportion of the muscle fibres became inactive within the motor unit (B, myopathic pattern) as distinct from a numerical decrease of active motor units in the muscle (C, discrete pattern). In the presence of axon degeneration fibrillation might be observed at rest (D, profuse fibrillation).

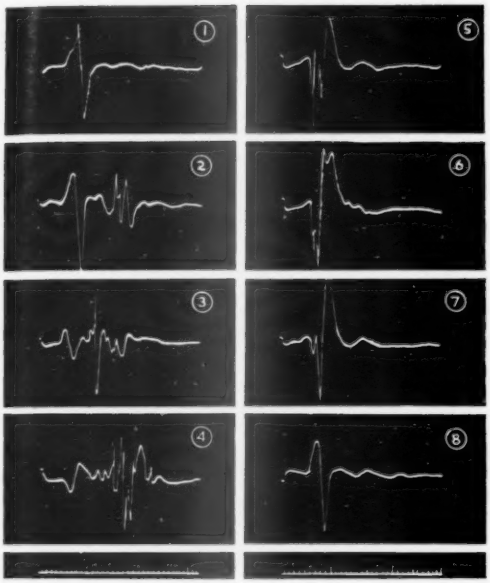



FIG. 3.—EMG tracings recorded on shock stimulation of the radial nerve with eight different positions of the needle electrode in extensor digitorum communis demonstrating temporal scatter of the activity in different motor units in polyneuritis. (Time scale in msec.)

subjected to a veritable electric storm, in form similar to the well-known electromyographic interference pattern on full volition. A little imagination will help you to conjure up the difference in the picture which would result if the electric storm abated by a progressively increasing percentage of idle muscle fibres in the motor units on the one hand, and a progressively increasing percentage of inactive whole motor units on the other hand.

In the first case the picture would pass from the normal interference pattern (Fig. 2A) to the myopathic pattern (Fig. 2B); in the second, from the normal interference pattern to a grossly decimated pattern (Fig. 2C) before you found yourself back in the silent world. In the presence of some denervated muscle fibres, fibrillation potentials might, of course, be detected at rest (Fig. 2D).

It would be tedious to describe all the other manifestations of pathology of the neuromuscular system for with very little further call on your imagination, you will be able to extend the analogy in which we have indulged, to myasthenia before and after Prostigmin or Tensilon exhibition; to myotonia; and to affections of the cord with their giant potentials and their fasciculation potentials.

What would happen if instead of volitional activity, nerve stimulation were substituted? With an adequate stimulus all the nerve fibres would be excited simultaneously at virtually the same level. The nerve impulses would then race down the fibres and the first to reach its group of muscle end plates would activate that motor unit which would be the first to break the latency. This would, of course, be the impulse set up in the fibre of largest calibre. Others would be propagated at a slightly reduced rate along fibres of lesser cross-section. All the same, the electric storm to which you would be subjected would be a violent, albeit a short-lived one—a matter of 10 msec. If for some reason a great discrepancy existed between the velocity of the winner, that of the loser and that of the intervening competitors, then you, as an intramuscular implant, would be tempest-tossed for some time, perhaps 20–30 msec. Of course, the longer the racing track, the longer you would have to wait for the stragglers.

That under certain conditions motor units respond in a staggered fashion although their nerve fibres have been stimulated simultaneously, can be seen from this series of eight action potentials, all from the same muscle in a patient with polyneuritis (Fig. 3). They were recorded electromyographically by means of a needle electrode inserted into the extensor digitorum communis while the radial nerve was being stimulated. The position of the needle was moved a few millimetres between stimulating pulses. It will be noted that the latency for the motor unit nearest the tip of the needle varies from 6 msec. for the first motor unit to fire off to 23 msec. for some of the late arrivals.

Again, when the stimulus applied to a nerve is progressively increased so that the fibres which are most easily stimulated are excited first, then successive records show the order in

which different motor units come into play. The final record is a kind of panorama of these sequential responses. Fig. 4 shows a sequence of four electromyographic responses picked up at the same time by means of a needle electrode (upper tracing) inserted in the extensor digitorum brevis, and a bipolar surface electrode (lower tracing) applied over it. The stimulus was increased between records.

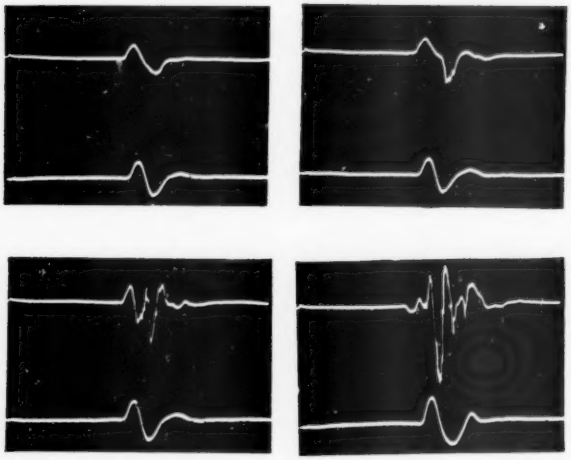
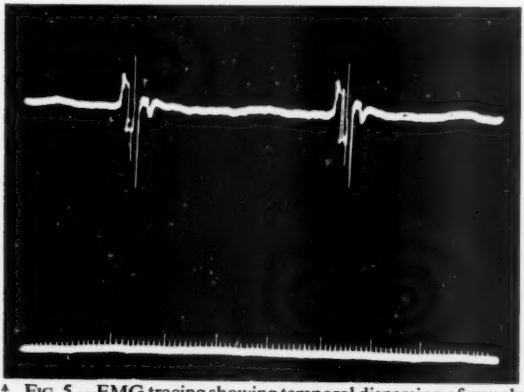


FIG. 4.—EMG tracings simultaneously recorded by means of a needle electrode (upper tracing) inserted in extensor digitorum brevis, and of surface electrodes (lower tracing) applied to the skin over this muscle during progressively increased stimulation of the anterior tibial nerve.

I should like to seize this opportunity of pointing out that although the surface electrode picks up the summated potentials, a filtering out of the high frequency components occurs. As the detection and analysis of this particular component is of value from a diagnostic angle, and is unfortunately obliterated by the use of surface electrodes, it follows that these electrodes cannot supplant needle electrodes for analytical purposes. However, just because of their power of picking up gross potentials of motor unit origin while rejecting finer potentials of muscle fibre origin, they possess a kind of coarse frequency discriminating faculty. For instance, the surface electrodes will readily pick up the discrete giant potentials encountered in a weak muscle where this is due to a motor neuron disease, but it will fail to pick up anv-



↑ FIG. 5.—EMG tracing showing temporal dispersion of muscle fibre activity within a motor unit on volition. (Time scale in msec.)

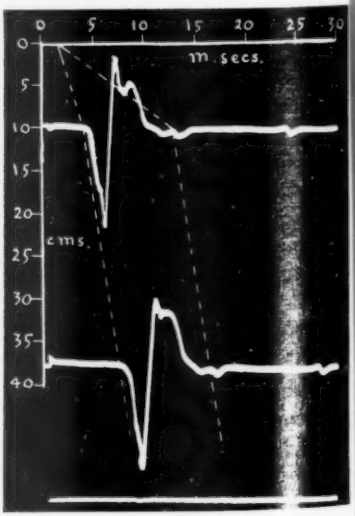



FIG. 6.—EMG tracing of responses in the first dorsal interosseus on stimulation of the ulnar nerve at the wrist and elbow.→ (Distances of points of stimulation from the pick-up electrode along ordinates in cm. Time relationships along abscissa in msec.)

thing in a muscle of similar weakness where this is due to a myopathy. In this sense surface electrodes could be regarded as a frequency discriminating device.

The question to be answered now is whether the temporal dispersion is of any significance. I must here remind you that two distinct types of temporal dispersion can occur. Temporal dispersion within a motor unit (Fig. 5), which can only be due either to unequal delay in neuromuscular transmission or—and this is more likely—to a differential velocity of conduction along the branches of the neuron distally, occurs mainly in the polyneuromyositis group of affections and in nerve regeneration, but it can also be observed at some stages in certain motor neuron affections of myelopathic nature. It is more readily detected during voluntary activity than on nerve stimulation.

The temporal dispersion of motor unit activity within a muscle of which I have already spoken on the other hand can be explained on the basis of differential velocity of conduction of nerve fibres, *qua* nerve fibres as distinct from axon branches. It is encountered in conditions where a motor nerve is subjected to chronic compression—as in the carpal tunnel syndrome. It is not easily observed on volition but is readily demonstrated on nerve stimulation. There appears to be no reason why in some conditions the two types of dispersion should not co-exist.

The cross-section of a nerve fibre is known to determine the velocity of the impulse propagation along it. A diminution of the calibre of a fibre reduces the speed and consequently increases the latency. Hodes *et al.* (1948), Lambert (1956), Simpson (1956) and Gilliatt and Thomas (1957) have drawn attention to gross increases in latency in some pathological conditions of the lower motor neuron and in nerve compression syndromes. They have shown how in the latter the pressure point may be located by stimulation at two points along the nerve.

Fig. 6 shows the electromyographic responses obtained in the first dorsal interosseus on stimulation of the ulnar nerve at the level of the wrist and the elbow. The two resulting electromyograms have been projected horizontally on to a graph in which the ordinates represent distances in centimetres from the point at which the needle electrode is embedded in the muscle while the abscissa is graduated in milliseconds. The position along the vertical occupied by each record shows at what distance stimulation was effected from the point of pick-up. In this particular case, the stimulation at the wrist and elbow was carried out approximately 10 cm. and 38 cm. from the point of the needle electrode respectively. The slope of the lines joining the beginnings and the ends of the potentials obtained is a measure of the velocity of conduction. It is interesting to note that those two lines are almost parallel, which would indicate that the velocities of conduction for all the neurons are approximately the same over the stretch between the elbow and the wrist.

If 2 msec. is taken as a generous estimate of the delay at the neuromuscular junction, the

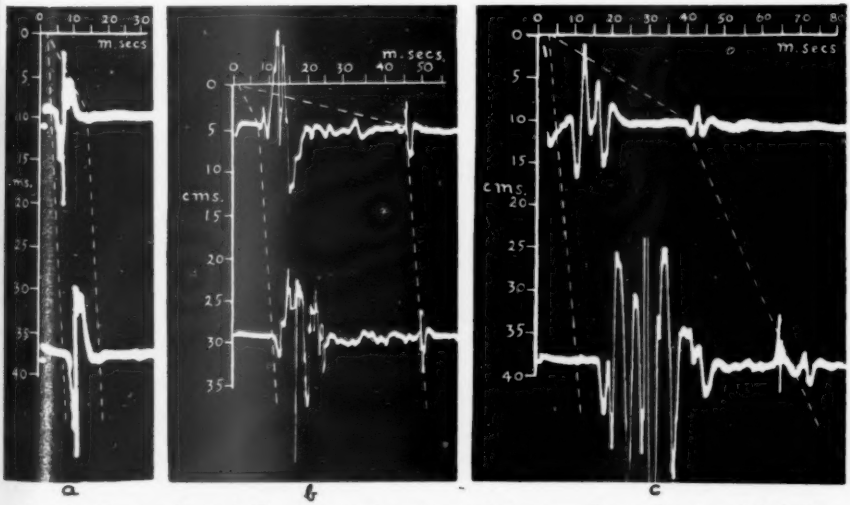



FIG. 7.—Construction as in Fig. 6 but tracings show variation according to situation of the lesion. A, normal; B, median nerve compression in carpal tunnel; C, ulnar nerve involvement in the epicondylar groove. (Time scale in msec.)

fact that both lines alter their slope to reach this point would indicate that not only does slowing down take place but that in the case of the motor units which account for the latter part of the response, the decrease in velocity is considerably greater (a reduction from 70 metres per second to 50 metres per second for the faster fibres, and from 70 metres per second to 9 metres per second for the slower ones).

Fig. 7 shows how three different conditions can affect the responses obtained on stimulation of a nerve at two levels in each case. The points to note in comparing these three sets of responses are:

(1) The latencies.

(2) The spread of the phenomenon on stimulation at the wrist.

(3) The spread on stimulation at the elbow.

Many of the perplexing phenomena encountered in electrodiagnosis appear to find their solution in the work of Paul Weiss. Briefly, he confirmed the hypothesis of Cook and Gerard (1931) and of Parker and Paine (1934) who postulated that the endoneural axoplasm of a motor neuron was formed in the anterior horn cell and was gradually propelled down the axon and that along the whole course of the axon a kind of metabolic consumption occurred.

Fig. 8 is an illustration from Weiss's paper (1956) on "The Life History of the Neuron"

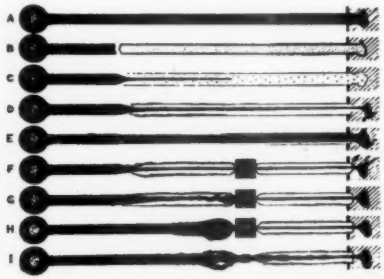



FIG. 8.—Diagrams of single nerve fibres in ordinary regeneration (B–E) and in regeneration combined with constriction (F–I), in the last case (I) followed by later release of the constriction. (From Weiss, P. (1956) The Life History of the Neuron, *J. chron. Dis.*, 3, 340, by kind permission.)

which graphically epitomizes his contentions. It is the result of six years' study involving experiments and observations on more than 100,000 nerve fibres. I can do no better than quote him. He says:

"You see here nine mature neurons, a normal one on top, the others in various stages of ordinary or modified regeneration. The nucleated cell bodies are on the left, the periphery is on the right. Lines B to E recapitulate the regenerative events following the crushing of a fibre. The proximal stump issues a thin filamentous outgrowth, which advances through the distal degenerated portion into the periphery (as seen in C), where it makes connexion with an old degenerated end-organ, as in D. The new sprout is then still very thin. Only gradually does it enlarge in width, eventually approximating full calibre. To achieve this, it must grow in protoplasmic mass about a hundredfold.

"It was this increase in girth which formed the subject of our investigations. By placing a constriction around a nerve, we can reduce the calibre of each constituent nerve fibre locally, as shown in lines F, G and H. If now we crush the fibre proximally to the constriction, a thin filament again regenerates through the constriction (in F). But as this filament keeps enlarging and attains the diameter of the constricted portion, a marked asymmetry begins to appear between the portions of the fibre lying proximally and those distally of the constriction, as you can see in G and H.

"The distal portion remains thin, and permanently so; while at the proximal end of the constriction, surplus neuroplasm piles up."

He concludes by saying:

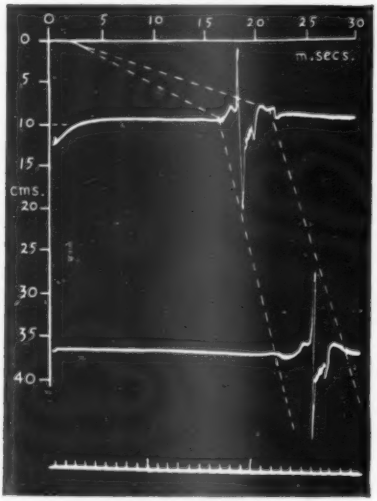
"The growth of the axon evidently occurs solely from its base, and the constriction, acting as a bottleneck, has throttled the supply of growing mass to the distal portion."

It is likely that when the position is such that the axon remains of small cross-section the velocity of conduction remains grossly reduced and the excitability low. The situation diagrammatically depicted here is probably very pertinent to that found in carpal tunnel compression, lesions of the ulnar nerve at the level of the elbow and in the palm of the hand, neurofibromata, and facial paralysis. In these conditions an increase in latency can almost invariably be demonstrated in some, if not all the motor units. In addition a considerable rise in the threshold may be observed distally to the lesion.

When dealing with a system like the one envisaged by Weiss where a cytoplasmic substance is produced at one end, propelled down a shaft and consumed at the other end, obstruction is not the only factor which will cause a depletion at the periphery. Deficient production and leakage along the conveyor or even excessive consumption would produce the same result.

Work carried out by Wohlfart (1957), Coërs (1955), and Woolf and Till (1955) has drawn attention to the dramatic phenomenon of sprouting of normal axons in the presence of denervated muscle and virtually effecting a collateral innervation of these with the formation of new neuromuscular junctions. The increase in the number of muscle fibres supplied by one motor neuron through this process must create gigantic motor units, and the caricature of the normal electromyographic pattern which we frequently observe may well be the result of this expansion coupled with temporal dispersion.

Fig. 9 shows the degree to which slowing down of impulse conduction can descend. These records were taken from a patient's first dorsal interosseus. He had a ganglion compressing the deep palmar branch of his ulnar nerve. The only motor units to respond showed a latency of 17 msec. on stimulation at the wrist, and 22 msec. on stimulation at the elbow. The reduction in velocity in this case is from 60 metres per second down to 7 and 5 metres per second distally to the lesion.




← FIG. 9.—Construction as in Figs. 6 and 7. EMG records show gross decrease in velocity of conduction along the deep palmar branch of the ulnar nerve due to compression by a ganglion. (Time scale in msec.)

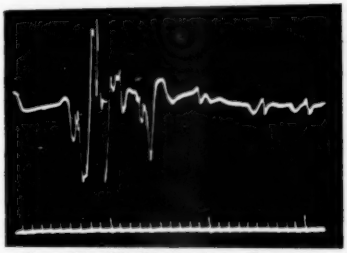


FIG. 10.—EMG tracing of response obtained in tibialis anticus on stimulation of the lateral popliteal nerve showing gross temporal scatter of the motor unit activity response.

Fig. 10 shows gross dispersion in the tibialis anticus on stimulation of the lateral popliteal nerve at the level of the knee-joint. The damage in this case resulted from ischæmia caused by a tight plaster.

Electrodiagnosis is not merely a technical procedure whereby an investigator, elaborately equipped, manages to manifest audibly and visually a sort of accepted hall-mark of a pathological condition. On the contrary it is in every sense a form of exploratory operation on a community of simple systems of which the individual and collective behaviour may have some diagnostic significance.

I use the word "exploratory" because the process of electromyography is not a static one. To extract the maximum information from it some precepts must be heeded. The most important of these is that the investigator should in mind withdraw from his surroundings and project himself on to the tip of the needle electrode, or under the surface electrode. He should be conscious of the machinery around him only in so far as it tells him of the electrical conditions prevailing there, and in so far as it is capable of making some permanent records or taking samples—like relevant snaps and films in the course of some quest.

The queries which have to be and can be answered as a result of this are many, and I can list only the more important, When the needle electrode is plunged into a muscle, insertion potentials may be noted. These may themselves suggest denervation or myotonia. After this, spontaneous activity may be registered in the shape of fibrillation, positive potentials or fasciculation. To increase the chances of finding out whether such phenomena are present it

is essential to move the needle electrode about with the object of tracking down any delinquent muscle fibre or eccentric motor unit. It must be remembered that a single fibrillating muscle fibre means that at least one muscle fibre is denervated, and this may be accounted valuable evidence.

At the inception of volitional activity the electromyographic pattern should present with small amplitude potentials, and on a progressive increase in activity larger and larger potentials should make their appearance until the normal full interference pattern is obtained. A deficiency of active motor units betrays itself either by gaps in the pattern which reveal the base line of the cathode ray trace or by the presence of an easily identifiable potential which dominates the picture. If an attempt is made at bearing down on the motor unit responsible for its presence, the potential may be found to be a very large one—so large that it may necessitate cutting down the amplification. From the point of view of population census, these tactics are invaluable. What you are really doing is locating a recognizable motor unit and finding out how near or how far from it other active motor units are on full volition. There may be no others within pick-up range of your electrode, in which case a discrete motor unit activity pattern results. This identifiable motor unit may have some interesting characteristics. It may show signs of temporal dispersion or give the impression that through accretion of muscle fibres, not originally part of it, it has become enlarged. Gentle transfixion of it during activity may reveal it to be a giant. At this point you may become conscious of an inconsistency. You may remember that when you stimulated the nerve supplying this particular muscle you obtained a response which justified your anticipating a far fuller pattern on volition than that obtained. This discrepancy between what could be demonstrated on stimulation and on volition is almost diagnostic of a myelopathic lesion just "north" of the anterior horn cells. I have coined the term "motor unit apraxia" to denote this set of conditions.

On the other hand, the electromyographic pattern on volition may be full and disturb the cathode ray base line throughout, but this may be made up of low amplitude short duration potentials. Such a picture spells an internal derangement of the motor unit and may be due to a myopathy, a distal neuronitis, a myositis or a myasthenia. The use of an *agent provocateur* may now be indicated. An intravenous injection of Prostigmin or Tensilon may dramatically improve the pattern if the deficiency is due to myasthenia gravis, or it may induce a denervated muscle fibre to fibrillate and thus act as an informer.

The time may now have come to stimulate the nerve and pick up the response electromyographically. I have already dwelt at some length on this, but I should like to draw attention to the fact that latency which has been given much prominence is not the only feature of importance. The motor unit which breaks the latency may well be one with an intact motor neuron. Far more importance attaches to the "also-rans". Indeed the stragglers may well be the ones on which a diagnosis has to be based.

Stimulation of the nerve by single shocks is not the only technique employed. Tetanizing currents can be made use of to demonstrate early fatigue in myasthenia or to precipitate a protracted myotonic contraction. Again, a defective power of accommodation such as is encountered in tetany can be brought to light by applying a progressively increasing direct current over the ulnar nerve at the elbow. Action potentials may then be picked up in the intrinsic muscles of the hand with quite low values of current. Moreover, these potentials frequently show signs of rapid repetition—doublets, triplets and quadruplets are frequently noted.

Exactly ten years ago (Bauwens, 1948) I expressed the belief that the clinical application of electrophysiology had immense potentialities, but that the value of the contribution it would ultimately bring to neurology would depend in a large measure on how well it was supported during its developmental stages by the tripod made of the neurologist, the neurosurgeon and the morbid pathologist. The intervening decade has done nothing to make me alter this belief except in so far as I can now say that this support together with a great deal of encouragement has been forthcoming.

## REFERENCES


Bauwens, P. (1948) *Proc. R. Soc. Med.*, **41**, 291.
Coërs, C. (1955) Thèse de Bruxelles.
Cook, D. D., and Gerard, R. W. (1931) *Amer. J. Physiol.*, **97**, 412.
Gilliatt, R. W., and Thomas, P. K. (1957) *Ann. phys. Med.*, **4**, 104.
Hodes, R., Larrabee, M. G., and German, W. (1948) *Arch. Neurol. Psychiat., Chicago*, **60**, 340.
Lambert, E. H. (1956) In: Clinical Examinations in Neurology. Mayo Clinic. Philadelphia; p. 313.
Parker, G. H., and Paine, V. L. (1934) *Amer. J. Anat.*, **54**, 1.
Simpson, J. A. (1956) *J. Neurol. Psychiat.*, **19**, 275.
Weiss, P. (1956) *J. chron. Dis.*, **3**, 340.
Wohlfart, G. (1957) *Neurology*, **7**, 124.
Woolf, A. L., and Till, K. (1955) *Proc. R. Soc. Med.*, **48**, 189.

# Section of Pædiatrics

President—A. Doyne Bell, M.A., D.M., F.R.C.P.

[*February* 28, 1958]

Meeting at the Hospital for Sick Children, Great Ormond Street, London

## Ulcerative Colitis in Childhood and a Follow-up Study [*Summary*]

By B. Schlesinger, O.B.E., M.D., F.R.C.P., and J. Platt, B.A., B.M., B.Ch., M.R.C.P.

*London*

Papers were read by Dr. B. Schlesinger discussing ulcerative colitis in childhood, and by Dr. J. Platt giving an account of a follow-up study. This study had been made by the speakers with Dr. Philip Benson and dealt with 60 children seen between 1938 and 1956 at the Hospital for Sick Children, Great Ormond Street, at University College Hospital and privately.

The possible occurrence of idiopathic ulcerative colitis in children was considered by Sir William Alchin in the course of an extensive discussion before the Society in 1909. However, the credit for the first definite account of the disease in childhood went to America (Helmholtz, 1923). Since that time further series had been published from America and Sweden (Langercrantz, 1955), but not as yet from this country.

The findings in the present investigation showed that the illness in childhood did not carry such an evil prognosis as was generally supposed, and supported the figures of Langercrantz.

Boys and girls were equally affected. The age of onset of symptoms was shown (Fig. 1) and attention was drawn to the 10% whose disease dated from the first year of life (Table I).

Table I.—Infantile Cases

| Name | Onset | Presentation | Therapy | Outcome | |
|---|---|---|---|---|---|
| M. W. | Under 4 months | Diarrhœa | Steroids | Died (perforation) | 11 months |
| C. W. | 2 weeks | Diarrhœa | Steroids | Symptoms | 13 years |
| L. J. | 1 month | Feeding difficulties | Steroids | Well | 8 months |
| B. R. | 3 months | Blood in stools | Ileostomy 1½ years; Colectomy 2½ years | Fairly well and awaiting anastomosis | 6 years |
| G. G. | 3 months | Diarrhœa and mucus | Non-specific | Well | 3 years |
| D. W. | 9 months | Diarrhœa, mucus and blood | Non-specific | Well (some diarrhœa) | 9 years |

Table II.—Initial Symptoms

| | | |
|---|---|---|
| Rectal bleeding alone .. | 10 | 17% |
| Rectal bleeding with diarrhœa and mucus .. | 19 | 32% |
| Diarrhœa without blood initially .. .. | 18 | 30% |
| Abdominal pain .. | 5 | 8% |
| Non-specific symptoms.. | 8 | 13% |
| | 60 | 100% |

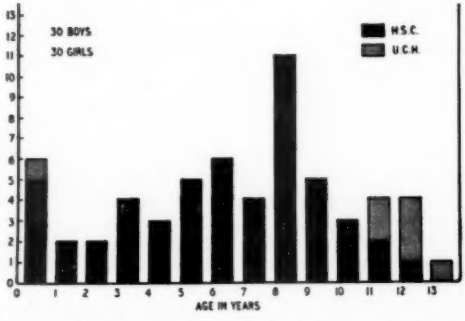



Fig. 1.—Ulcerative colitis (children): age at onset in 60 cases. ⟶

The mode of onset was given (Table II) and emphasis placed on the fact that rectal hæmorrhage was at first the sole symptom in 17%. A further 21% had abdominal pain or constitutional disturbance for weeks or months before the stools became frequent or abnormal.

Dr. Schlesinger discussed the emotional factors involved. Although there was a disturbed family background or some calamity prior to the onset of symptoms in a third of the cases, it was also true to say that two-thirds of the children seemed to enjoy a happy, stable home. Nevertheless, the children did tend to show certain characteristics, particularly undue conscientiousness, with concern over school performance and fastidious cleanliness. Frequently they seemed unduly dependent upon, or at odds with, one parent—usually the mother. They found difficulty in expressing their emotions by word or deed, and emotional crises tended to be manifest by a relapse of their colitis. Almost one-quarter of the children were Jewish; this was four times the average proportion of Jewish children amongst the total admissions to the Hospital for Sick Children. There was a family history of ulcerative colitis in 17% of near relatives in the series. This included a pair of brothers and a brother and sister. The incidence was greater than in other published figures.

On examination the children were notably above average in intelligence and below average in weight. Tachycardia was the only other striking physical sign apart from the appearance of the stools.

Sigmoidoscopic and barium enema studies were incomplete. However, they affirmed that, whereas the rectum and sigmoid colon were occasionally spared, it was common to find granular proctitis in the absence of X-ray changes. The disease could spread later to involve the whole colon. The ileum was demonstrably affected in 3 cases.

The usual complications had occurred and the incidence of arthritis in 20% of cases was emphasized. It differed from rheumatoid arthritis in its distribution and course.

The results of treatment by steroids and surgery were given (Tables III and IV). Some of

TABLE III.—STEROID THERAPY

| | | |
|---|---|---|
| No improvement | .. | 3 |
| Remitted | .. .. | 5 |
| Died while receiving | .. | 2 |
| Still receiving: | | |
| Symptoms 5 | | |
| Well 6 | .. | 11 |
| | | 21 |

TABLE IV.—SURGERY

| | | | | | |
|---|---|---|---|---|---|
| Obligatory ileostomy | .. .. .. .. | | | | 1 |
| Ileostomy and colectomy | .. .. .. | | | | 1 |
| Anastomosis: | | | | | |
| (1) without colectomy | .. .. .. | | | 1 | |
| (2) two-stage | .. .. .. .. | | | 4 | |
| (3) one-stage | .. .. .. .. | | | 4 | |
| | | | | — | 9 |
| Appendicostomy | .. .. .. .. .. | | | | 1 |
| | | | | | 12 |

the limitations of steroid therapy were overcome by the use of hydrocortisone hemisuccinate in a rectal drip.

Dr. Robin Higgins had undertaken psychotherapy with 5 children. One girl had had an effective remission dating from the treatment. She was the only child for whom a full course had been achieved. Aside from this, the value of "superficial" psychotherapy, especially continued relationship with a single physician, was emphasized.

A classification of the cases and their state at follow-up was shown (Table V). The health

TABLE V.—PROGNOSIS RELATED TO CLINICAL COURSE

| | | | | |
|---|---|---|---|---|
| (1) *Acute fulminating, death within one year* | .. | | 1 | 2% |
| (2) *Chronic intermittent* | (*a*) Dead .. | 3 | | |
| | (*b*) Symptoms | 9 | | |
| | (*c*) Well .. | 18 | | |
| | | — | 30 | 50% |
| (3) *Chronic continuous* | (*a*) Dead .. | 1 | | |
| | (*b*) Symptoms | 12 | | |
| | (*c*) Well | 8 | | |
| | | — | 21 | 35% |
| (4) *Single* attack with complete remission | .. | | 4 | 6·5% |
| (5) Well on steroids | .. .. .. | | 4 | 6·5% |
| | | | 60 | 100% |

of those who had or would have reached the age of 20 was discussed. 2 of them had died of carcinoma of the colon (ages 23 and 27) after a period of several years of alleged freedom from symptoms of their ulcerative colitis. This gave an incidence of 14% for malignant change amongst those who had passed their 20th birthday and retained their colon.

Aside from this danger, it was important to realize that 55% of cases were well ten years after the start of their symptoms, even though a few had had protracted or severe illness during childhood. Unless the disease could not be controlled by medical treatment there seemed to be no indication for surgery until the age of 14 or 15. Thereafter, symptoms, if still present, would persist or the child would die unless colectomy—preferably with ileo-rectal anastomosis—was undertaken.

The speakers thanked all the physicians and surgeons, many of whom were present, who had so generously provided follow-up data and access to those children who were now their patients.

## REFERENCES

ALCHIN, W. (1909) *Proc. R. Soc. Med.*, **2**, 59.
HELMHOLTZ, H. F. (1923) *Amer. J. Dis. Child.*, **26**, 418.
LANGERCRANTZ, R. (1955) *Acta pædiat., Stockh.*, **44**, 302.

## DEMONSTRATIONS

**Absent Abdominal Muscles.**—Mr. D. INNES WILLIAMS and Dr. S. LEIBOWITZ.

**The Dietary Treatment of Phenylketonuria.**—Professor ALAN A. MONCRIEFF and Dr. L. I. WOOLF.

**Mast Cell Disease.**—Dr. E. STROUD and Dr. M. LEES.

**Œdema and Turner's Syndrome.**—Dr. E. STROUD.

**Clinico-pathological Study of Complications and Prognosis of Hypophosphatasia.**—Dr. B. SCHLESINGER, Dr. J. LUDER and Dr. M. BODIAN.

**Sickle-cell Anæmia.**—Dr. J. LUDER.

**Electromyography, Especially in the Diagnosis of "Floppy Children".**—Dr. A. T. RICHARDSON and Dr. E. D. CAMPBELL.

**Diagnosis of Obstructive Jaundice in Early Infancy.**—Dr. G. H. NEWNS, Dr. M. BODIAN and Mr. H. H. NIXON.

**Treatment of Perthes Disease.**—Mr. G. C. LLOYD ROBERTS.

**Natural History of Untreated Hydrocephalus (An Interim Report).**—Dr. K. M. LAURENCE and Mr. S. H. COATES.

[*March* 28, 1958]

**Recurrent Hypertrophic Polyneuritis.**—PHILIP R. CLAY, M.R.C.P. (for HUGH ELLIS, M.D.).

D. H., male, aged 12 years.

*History.*—Age 1–6 years eczema and asthma. General health not severely affected. June 1951, aged 6 years: Had coryza, headache and fever followed by progressive symmetrical muscle weakness most marked peripherally, with aching of arms and legs.

*Family history.*—Asthma. Eczema.

*On examination* 31.7.51.—Ichthyotic skin, with some pigmentation. Arms: Slight wasting. Marked weakness of all movements. Legs: Some wasting of calves with gross weakness of dorsiflexion of feet. Reflexes: Triceps-jerks only elicited. No sensory loss.

*Investigations.*—C.S.F.: (1) Protein 115 mg.%, no cells. (2) Protein 135 mg.%, 3 cells. Urine: Coproporphyrin content less than 20 micrograms/twenty-four hours. Fully recovered by October 1952.

*June* 1954 *to December* 1955: 3 relapses—2 following dental extraction.

*Fourth relapse March* 1956: Admitted to hospital August 1956—no response to Disodium Calcium Versenate and large doses of vitamin B. Almost fully recovered by May 1957.

*Fifth relapse June* 1957: Severe motor paralysis especially peripherally. Noted to have thickening of ulnar and spinal accessory nerves.

*Investigations.*—C.S.F. protein 200 mg.%. W.R. and Kahn negative. Serum potassium 4·7 mEq./l. EMG: Extensor digitorum middle finger and extensor hallucis longus—somewhat atypical curves of denervation. Urine chromatography (Professor Dent): No abnormality.

12.10.57: Influenza. Four days later rapid recovery. Almost complete in five days.

*Sixth relapse* 28.2.58: Noted to have fasciculation of deltoids. C.S.F. protein 120 mg.%. Agglutination to *Brucella abortus* negative.

## DISCUSSION

Recurrent polyneuritis due to other than obvious causes such as poisons has been described fairly extensively in the literature.

According to Harris (1922) Grocco was the first to describe a case in 1885.

A number of cases have been recorded associated with pregnancy and the puerperium, first by Rossolimo in 1899 in a woman who had an attack in childhood with two relapses of polyneuritis in the puerperium associated with sensory changes, fibrillary twitchings, nystagmus, loss of reflexes and amyotrophy. In addition there was hypertrophy of *radial and ulnar nerves.* Other cases associated with the puerperium have been described by Batten (1912) and Ungley (1933).

A seasonal incidence was noted by Holmes (1928) in one case and he quoted another

case of Thomas' with five relapses in June. Holmes also quoted 2 cases with no seasonal incidence, the most striking feature in his own words being "rapidity and completeness of recovery". In 1921 Nattrass described a case of motor polyneuritis in an 18-year-old boy who had had two previous attacks. The C.S.F. protein was normal. Like the case described by Rossolimo, this boy had marked nerve hypertrophy. A similar case was described by Harris and Newcomb in 1929 which showed gross nerve hypertrophy at post-mortem. Nattrass felt that his case was a variant of progressive hypertrophic polyneuritis as described by Déjerine and Sottas in 1893.

In 1932 Wolff *et al.* reviewed the literature of progressive hypertrophic polyneuritis including the cases of Nattrass and Harris and Newcomb among 40 cases. In one of his own cases, a pure motor polyneuritis, the C.S.F. protein was markedly raised.

This child most closely resembles the cases of Rossolimo, Nattrass and Harris and Newcomb, though in this case the C.S.F. protein has been persistently raised. It has not been examined in a remission. No ætiological factor has been discovered. On one occasion he improved dramatically following influenza, in contrast to one of Wolff's cases which rapidly deteriorated. This child says he is weaker in hot or cold weather and when he gets worried.

Cortisone has been reported to have benefited cases of the Guillain-Barré syndrome, and in reviewing the literature Jackson *et al.* (1957) quote 68 cases, 50 of whom had shown definite improvement. Cortisone has not been used because he has repeatedly improved spontaneously and it would be difficult to assess the effect of cortisone in this case. In addition the question of approaching puberty has to be considered.

## REFERENCES


BATTEN, F. E. (1912) *Proc. R. Soc. Med.*, **6**, Sect. Neurol. 62.

DÉJERINE, J., and SOTTAS, J. (1893) *C.R. Soc. Biol., Paris*, **5**, 63.

HARRIS, W. (1922) *Brain*, **45**, 415.

——, and NEWCOMB, W. D. (1929) *Brain*, **52**, 108.

HOLMES, G. (1928) In: Modern Medicine—its Theory and Practice. Edited by W. Osler and T. McCrae. 3rd Ed. London; Vol. 6, p. 451.

JACKSON, R. H., MILLER, H., and SCHAPIRA, I. C. (1957) *Brit. med. J.*, i, 480.

NATTRASS, F. J. (1921) *J. Neurol. Psychopath*, **2**, 159.

ROSSOLIMO, G. (1899) *Rev. Neurol.*, **7**, 558.

UNGLEY, G. C. (1933) *J. Neurol. Psychopath.*, **14**, 15.

WOLFF, A., RUBINOWITZ, A. H., and BURCHELL, S. C. (1932) *Bull. neurol. Inst. N.Y.*, **2**, 373.


**Syndrome of Osteoporosis, Calcification of the Basal Ganglia, Dwarfism, Mental Retardation and Ventricular Septal Defect.**—P. F. BENSON, M.R.C.P. (for R. E. BONHAM CARTER, F.R.C.P.).

J. C., female, aged 12.

Born two weeks prematurely.

*Family history.*—Her parents and 14-year-old sister are of normal height and development.

*History.*—At 2 years of age she was taken to Great Ormond Street Hospital because of failure to grow. A diagnosis of hypopituitarism was made. Her milestones were retarded, she sat up at 9 months and walked at 19 months. She has frequent attacks of bronchitis and becomes dyspnœic and mildly cyanotic on exercise.

*On examination.*—Small but normally proportioned. Height and weight both below the third percentile. She has pubic and axillary hair and early breast development. No pigmentation. Slight thoracic scoliosis and a short neck. Small head (circ. 18 in.). No webbing of neck. C.V.S.: pulses normal. B.P. 105/70; apex beat fifth left intercostal space, anterior axillary line; second pulmonary sound split; loud systolic murmur maximal in the third left intercostal space. Lungs: bilateral rhonchi and coarse crepitations.

*Investigations.*—X-rays (Dr. C. J. Hodson): Spine and long bones: osteoporotic. (Spine: Fig. 1). Skull: calcification of the basal ganglia (Figs. 2 and 3). I.V.P.: small rounded opacity in the region of the right renal pelvis, possibly a calculus. Excretion and urinary tracts normal. Bone age: 11 years. Skulls of parents and sister: no intracranial calcification. Cardiac catheterization (Dr. J. W. Brown, Sheffield): ventricular septal defect. Calcium balance 10 mg. positive. Fat balance normal. Radio-iodine uptake 40% normal. Vaginal cell smear œstrogenized. Urinary gonadotrophic hormone normal. Serum calcium 9·8 mg., phosphorus 5·0 mg., alkaline phosphatase 14·0 K.A. units/100 ml. Chromosomal sex (buccal smear) female. Urine and blood counts normal. Maximum urea clearance 39%. Urine concentration test: sp. gr. 1020. Urine dilution test: sp. gr. 1003. Blood urea and electrolytes normal. Plasma proteins and urinary chromatogram normal. Toxoplasmosis tests (Dr. I. A. B. Pilthie) negative.



FIG. 1.



FIG. 2.



FIG. 3.

## DISCUSSION

Calcification in the basal ganglia is often found microscopically in otherwise normal adult brains (Foley, 1951). Only very rarely, however, is it gross enough to be visualized radiologically. Most of these cases have been associated with hypoparathyroidism (Albright *et al.*, 1942). Toxoplasmosis (Sutton, 1951) and bilateral cerebral angiomas are other causes. There remains a group of idiopathic bilateral symmetrical calcification of the basal ganglia of which the case reported is an example. A search of the literature (*see below*) has not revealed any other cases in children without a severe neurological disorder or associated with congenital heart disease.

## REFERENCES


ALBRIGHT, F., BURNETT, C. H., SMITH, P. H., and PARSON, W. (1942) *Endocrinology*, **30**, 922.

EATON, L. M., CAMP, J. D., and LOVE, J. G. (1939) *Arch. Neurol. Psychiat., Chicago*, **41**, 921.

FOLEY, J. (1951) *J. Neurol. Psychiat.*, **14**, 253.

FRITZSCHE, R. (1935) *Schweiz. Arch. Neurol. Psychiat.*, **35**, 1.

KASANIN, J., and KRANK, R. P. (1935) *Arch. Neurol. Psychiat., Chicago*, **34**, 164.

MATTHEWS, W. B. (1957) *J. Neurol. Psychiat.*, **20**, 172.

NEILL, C. A., and DINGWALL, M. M. (1950) *Arch. Dis. Childh.*, **25**, 213.

REND, C. W., OLSEN, C. W., and COURVILLE, C. B. (1943) *Bull. Los Angeles neurol. Soc.*, **8**, 118.

SAMMET, J. F., and BUCY, P. C. (1951) *Amer. J. Roentgenol.*, **66**, 880.

STROBOS, R. R. J., DE LA TORRE, E., and MARTIN, J. F. (1957) *Brain*, **80**, 313.

SUTTON, D. (1951) *Brit. J. Radiol.*, **24**, 31.

**Martin's Syndrome Diagnosed by Finding Heinz Bodies in the Peripheral Blood.**—D. G. COTTOM, M.R.C.P. (for R. E. BONHAM CARTER, F.R.C.P.).

S. W., female. Age at death 4 months.

First child of healthy parents, born after a normal full-term pregnancy, birth weight 6 lb. 7 oz. She was noticed to be cyanosed on the second day of life, and to become breathless during feeding. Grade I systolic murmur audible at left sternal edge; pulmonary second sound diminished. Femorals easily palpable.

*Investigations.*—Chest X-rays: Heart lying transversely, with oligæmic lung fields and a right-sided aortic arch. Liver on the left (Fig. 1). ECG: Considerable left ventricular hypertophy. Diagnosis: ? Tricuspid atresia. Hb 120%; numerous normoblasts; many erythrocytes contained Heinz bodies. Diagnosis: ? Martin's syndrome.

Developed cardiac failure, and responded only partially to treatment with Digoxin, aminophylline, &c.

*Operation* (Mr. D. Waterston).—Blalock's operation through right thoracotomy. Considerable improvement following operation, and although no anastomotic murmur could be heard, the cyanosis was much less.

Sent home when 8 weeks old. Readmitted two months later in gross cardiac failure. She had a sudden cyanotic attack and died.

Autopsy showed the complex of abnormalities first described by Martin in 1826. They included: Situs inversus abdominalis; absent spleen; universal mesentery; congenital heart disease with defects of both auricular and ventricular septa and atresia of tricuspid valve and pulmonary trunk; double inferior vena cava.

## DISCUSSION

The interest of this syndrome lies in the ability to predict a series of complex congenital anomalies from an examination of the blood (Gasser and Willi, 1952). Since it involves so many systems it is possible to determine with fair accuracy the time at which damage to the fœtus is thought to occur. Towers and Middleton (1956) suggest that it is as early as the twenty-fourth to twenty-seventh day.

The heart is functionally bilocular. The R.A. receives a normal S.V.C. but only a short I.V.C. from the left lobe of liver, the main I.V.C. entering the L.A. There is a large intra-auricular septal defect, no tricuspid orifice, the R.V. is represented by a small slit and has no communication with the atria but receives blood from the L.V. and expels it via an overriding aorta. The pulmonary trunk is atretic, the only access to the pulmonary artery being via a large patent ductus arteriosus (Fig. 2). Ivemark (1955) collected 69 cases of congenital heart disease associated with asplenia and this type of defect was present in 41.

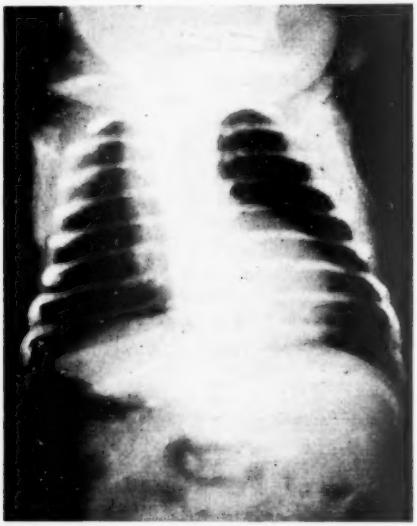


FIG. 1.—X-ray showing situs inversus abdominalis together with oligæmic lung fields.

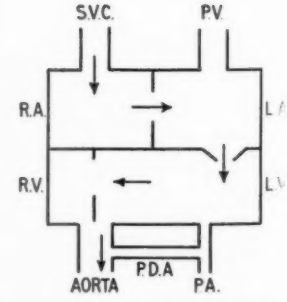



FIG. 2.—To show probable blood flow.

## REFERENCES

GASSER, C., and WILLI, H. (1952) *Helv. pædiat. Acta*, **7**, 369.
IVEMARK, B. I. (1955) *Acta pædiat., Stockh.*, **44**, Suppl. 104.
MARTIN, G. (1826) *Bull. Soc. anat. Paris*, **1**, 39.
TOWERS, B., and MIDDLETON, H. (1956) *J. Path. Bact.*, **72**, 553.


**Juvenile Disseminated Sclerosis.**—R. H. R. WHITE, M.A., M.B., M.R.C.P., D.C.H. (for P. R. EVANS, M.D., M.Sc., F.R.C.P.).

M. M., male, born 28.12.44.

*Family history.*—Parents healthy. Sister had primary tuberculosis in 1947. No family history of neurological disease.

*Previous history.*—Admitted to hospital August 1950 with erythema nodosum associated with streptococcal tonsillitis and meningism. Mantoux positive, chest radiograph normal; C.S.F. normal.

*Present illness, treatment and progress.*—Readmitted April 1952, five weeks after tonsillectomy, with two days' history of giddiness and twitching of left side of face; found to have right hemiparesis involving mouth and both limbs, and minimal impairment of position sense of the right hand and foot. C.S.F. normal. Gradual improvement occurred but slightly increased muscle tone, hyperreflexia and upgoing toe persisted on right side.

February 1953: Paronychia incised, under general anæsthetic. Three days later developed neck stiffness and a flaccid left hemiparesis without facial involvement, left arm being extremely weak, with absent reflexes. Signs on right side unchanged. Both plantar reflexes extensor. C.S.F. showed 79 lymphocytes per c.mm., protein 57 mg.%, sugar 80 mg.%. Again, incomplete recovery.

May 1954: Headache and giddiness, "doubtful nystagmus and ataxia of left arm"; C.S.F. normal.

May 1957: Three days' chest pain and slight fever, followed by complete paraplegia with double incontinence, flexor withdrawal reflexes, total analgesia below T.V. 8, and partial loss of thermal and vibration sensation; tactile sensation normal. C.S.F. showed 117 lymphocytes per c.mm., protein 60 mg.%. Chest radiograph normal. W.B.C. showed slight granulocytosis. Treated with prednisolone for twenty-eight days (40 mg. daily for first twelve days). Showed progressive and almost complete recovery from the acute paraplegia.

July 1957: Acute pain behind left eye for three days. Fundi, visual fields and acuity normal.

March 1958: Septic finger, severe attacks of nausea and giddiness on turning head. Gait unsteady, fell to right. Nystagmus vertically on upward gaze, to right on lateral gaze. Hearing normal. C.S.F. showed 18 lymphocytes, protein 60 mg.%, Lange normal. Rapid recovery.

*Present condition.*—Residual bilateral hemiparesis, R > L, with underdeveloped right hand and shortened right leg; slight cerebellar ataxia of right arm. The only subjective disability is difficulty with fine movements of right hand (e.g. writing) and barely noticeable dragging of right leg. No emotional, speech or visual disturbance.

### DISCUSSION

Since 7 years of age, this boy has had a chronic, remitting, episodic illness. Two episodes were somewhat indistinct but the remaining four were associated with definite neurological abnormalities and three with changes in the cerebrospinal fluid. Each can be attributed to a lesion in a different anatomical site. Three attacks were preceded by surgical trauma, anæsthesia or infection; in the remainder there were no obvious precipitating factors. Recovery was incomplete in the first two attacks, although the residual disability is slight. This clinical picture is characteristic of disseminated sclerosis and the absence of visual disturbance does not preclude the diagnosis. It is unlike that of diffuse sclerosis, in which there is usually progressive deterioration without remission, and predominance of cerebral cortical lesions.

The pain and fever which preceded the paraplegia, in May 1957, and the cellular reaction of the C.S.F. are more in keeping with a diagnosis of acute disseminated encephalomyelitis. The response to prednisolone may have been coincidental but, if consequential, would possibly favour this diagnosis. On the other hand, it is usually a self-limiting disease which does not relapse.

*Age of onset.*—Out of 1,107 reported cases of disseminated sclerosis, symptoms began before the age of 10 years in 2% and between 10 and 20 years in 14% (Wilson, 1954; Merritt, 1955). Müller (1951) reviewed 810 cases and found an onset before 15 years in 6%. However, McAlpine and Compston (1952) found an incidence of only 1·4% beginning between 10 and 14 years, and Carter (1946) noted a sharp increase in incidence between 16 and 17 years.

In spite of its occurrence in childhood, standard pædiatric textbooks make little or no

reference to disseminated sclerosis. The diagnosis is, admittedly, challengeable without histological proof but, as a purely *clinical* diagnosis, it is probably acceptable in the present case.

REFERENCES

CARTER, H. R. (1946) *Amer. J. Dis. Child.*, **71**, 138.
MCALPINE, D., and COMPSTON, N. (1952) *Quart. J. Med.*, **21**, 135.
MERRITT, H. H. (1955) Textbook of Neurology. London.
MÜLLER, R. (1951) *Arch. Neurol. Psychiat., Chicago*, **66**, 561.
WILSON, S. A. K. (1954) In: Neurology. Edited by A. N. Bruce. London.

**Vitamin-D-resistant Rickets with Craniostenosis.**—K. HUGH-JONES, M.D., M.R.C.P. (for C. F. HARRIS, M.D., F.R.C.P.).

C. R., male, now aged 4 years 3 months. Born at term following a normal pregnancy, weighing 9½ lb. Breast fed for nine months.

Adexolin given from the age of 4 months, 1,200 I.U. daily, from 6–14 months 1,600 I.U. and from 14–18 months 2,800 I.U. daily.

Admitted aged 18 months with a history of bowed legs since birth because adequate intake of vitamin D had had no effect on his rickets.

*Family history.*—First child of healthy parents who are first cousins. Father had slight bowing of the legs when 5 but X-rays of legs and skull are now normal, as are those of his wife.

*On examination.*—May 1955, aged 18 months. Skull circumference 18½ in., sutures and fontanelles closed, skull thickened along the line of the sutures, some frontal bossing, rickety rosary, early Harrison's sulcus and also considerable epiphyseal thickening at the wrists and knees and bowing of the tibiæ and femora. The humeri were a little short. There was moderate hypotonia. Teeth erupted normally (Fig. 1).

*Investigations.*—Blood urea 24 mg. per 100 ml., serum calcium 11 mg. per 100 ml., serum inorganic phosphate 3·2 mg. per 100 ml., serum alkaline phosphatase 42 K.A. units, serum chlorides 104 m.Eq./l., alkali reserve 21·5 m.Eq./l. Urine contained no protein or reducing substances. Chromatography revealed a normal amino-acid excretion. Sp. gr. 1000–1028; 75% water load excreted in three hours. X-rays showed gross rickets; also a rather coarse trabecular pattern (Fig. 2). The skull shows fairly dense bone in the base and vault and an open coronal suture (Fig. 3). Calcium and phosphate balances aged 18 months, having been taking vitamin D 2,800 I.U. daily, showed 50% of calcium intake excreted in the fæces, 1% in the urine, 49% retained. 48% of phosphate intake retained but only 18% excreted in the fæces and 34% in the urine.

*Treatment and follow-up.*—He has been given calciferol 50,000 I.U. daily. There has been frequent biochemical control. On only one occasion was he hypercalcæmic when the level was 13·2 mg. per 100 ml. Rate of growth has been nearly normal but height is only in the tenth percentile. Weight gains satisfactory. Skull circumference has increased by 1 inch from the age of 18 months to 4 years 3 months; this is a normal increment. The skull is now even more thickened along the suture lines. X-rays of the skull since the age of 3 have shown the sutures to be closed (Fig. 4). There have been no symptoms of raised intracranial pressure and the optic discs are normal.

DISCUSSION

The craniostenosis was not thought to be due to treatment because the suture lines were thickened and raised when first seen. Also treatment has never been excessive and there have been no symptoms of hypercalcæmia and on only one occasion has the serum calcium level been raised. It would seem therefore that this boy presented with these two abnormalities, an association which has been recorded previously. Imerslund (1951) reported a child with familial vitamin-D-resistant rickets, short humeri and femora and scaphocephaly, his mother being similarly affected. The child required a decompression craniotomy when aged 23 months because of early papillœdema. Coleman and Foote (1954) reported a boy with scaphocephaly and resistant rickets and again the mother was similarly affected. Pedersen and McCarrol (1951) in a review of 25 cases think that children with vitamin-D-resistant rickets have a characteristic skull shape with increased anteroposterior and decreased transverse diameters though they make no mention of craniostenosis. They also stress the coarse and broad trabecular pattern seen on the X-rays of long bones. The photographs of Albright's original case certainly look as though he had scaphocephaly. Engfeldt, Zetterström, Winberg and others in Stockholm consider from their metabolic studies and examination of microradiographs in cases before and after treatment that a part of this condition is due to a primary skeletal abnormality which is unaffected by vitamin D. These associated bony abnormalities and the odd, coarse trabecular pattern on X-ray would lend support to this hypothesis.

It was felt in this child that as there were no symptoms of raised intracranial pressure, and most of his brain growth had already occurred and it was seen that his skull was increasing



FIG. 1.—Child, aged 18 months.

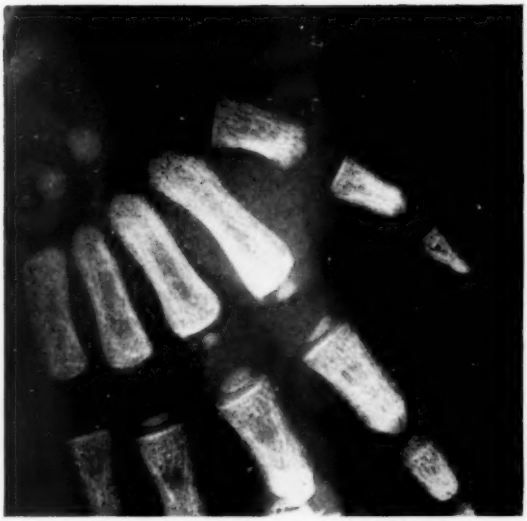


FIG. 2.—X-ray wrist aged 18 months showing rickety changes and coarse trabecular pattern.



FIG. 3.—Skull X-ray aged 18 months. Dense bone in base and vault.

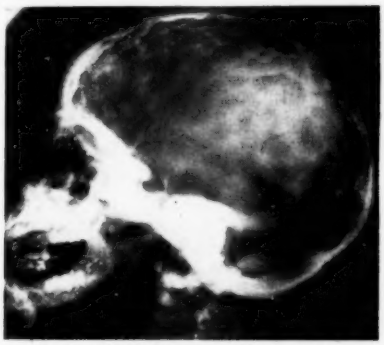


FIG. 4.—Skull X-ray aged 3 years. Coronal suture now completely closed. Lambdoid suture nearly closed.

in size, it was justifiable to watch progress rather than advise surgical correction of his craniostenosis. There was a suggestion from his parents that he was not as bright and intelligent or so well behaved as he used to be, which may be an early symptom due to the craniostenosis; a fact which has only been realized by operating on cases and observing the improvement afterwards (Ingraham, 1948).

In general, the meeting was in agreement with our expectant policy, provided a very close watch was kept on the child both biochemically and clinically.

## REFERENCES


ALBRIGHT, F., BUTLER, A. M., and BLOOMBERG, E. (1937) *Amer. J. Dis. Child.*, **54**, 529.
COLEMAN, E. N., and FOOTE, J. B. (1954) *Brit. med. J.*, i, 561.
ENGFELDT, B., ZETTERSTRÖM, R., and WINBERG, J. (1956) *J. Bone Jt. Surg.*, **38** (A), 1323.
IMERSLUND, O. (1951) *Acta pædiat., Stockh.*, **40**, 449.
INGRAHAM, F. D. (1948) *Surgery*, **24**, 518.
PEDERSEN, H. E., and MCCARROL, H. R. (1951) *J. Bone Jt. Surg.*, **33** (A), 203.
WINBERG, J., BERGSTRAND, C. G., ENGFELDT, B., and ZETTERSTRÖM, R. (1954) *Acta pædiat., Stockh.*, **43**, 347.
ZETTERSTRÖM, R., and WINBERG, J. (1955) *Acta pædiat., Stockh.*, **44**, 45.

**Thoracic Neuroblastoma, Treated with Vitamin $B_{12}$.**—O. D. FISHER, M.R.C.P.

M. S., female, aged 5.

Admitted November 1956 with complete weakness of both lower limbs and absence of reflexes. Sensory loss in both legs, extending to the hip on the left side and the nipple line on the right. X-ray chest revealed a thoracic mass. Laminectomy, January 1957, revealed a fleshy extradural tumour, which biopsy showed was a neuroblastoma.

*Treatment.*—Vitamin $B_{12}$ over twelve months was followed by a gradual but marked reduction in size of the thoracic tumour, and recovery of power in both legs.

*Comment.*—A thoracic neuroblastoma which has responded to vitamin $B_{12}$ without surgical excision or irradiation. A further point of interest is the lower motor neuron type of paralysis with a high thoracic tumour.

**Hypertrophy of Right Calf Muscles.**—O. D. FISHER, M.R.C.P.

B. R., female, aged 10.

*History.*—Seen in August 1957 as her right calf was said to be larger than the left for the past three months. No other complaints.

*On examination.*—Healthy child with hypertrophy of right calf muscle. No mass present in the muscle. Right calf one inch greater in circumference than the left, the muscle feeling rather firm. Reflexes appeared normal in both legs.

*Investigations.*—E.S.R. 14 mm. in one hour (Wintrobe); urinary chromatogram normal; urinary creatine and creatinine normal. Rose's D.A.T. and euglobulin tests negative; C-reactive protein absent; protein electrophoresis normal pattern. EMG: left calf shows a normal interference pattern. Right calf: no spontaneous activity. Action potentials small in amplitude and duration. Conclusively in favour of a myopathy.

*Biopsy.*—Superficial and deep surfaces of both gastrocnemius and soleus explored. "Considerable loss of striation and increase in number of nuclei in muscle fibres, in keeping with pseudohypertrophic muscular dystrophy."

Following discussion, subsequent investigations showed no difference in the skin temperature of each leg and the serum aldolase was not raised.

**L.E. Cell Phenomenon Associated with Chronic Hepatitis.**—C. UPJOHN, M.D. (for J. N. O'REILLY, D.M.).

B. B., female, aged 13½.

*History.*—Aged 10 years had an attack of abdominal pain, vomiting and fever up to 101° F. for one week, for which there was no clinical cause, and investigation was negative apart from E.S.R. 35 mm. in one hour (Westergren).

Three years later again unwell, initially with sore throat and enlarged cervical glands. During the next six weeks her condition deteriorated steadily with vomiting, pains in elbow and shoulder joints and hands. Pain subsided and then recurred again after three weeks. Increasing fever latterly and a mild degree of jaundice developed. A skin eruption like erythema nodosum developed over her shins.

*On examination.*—Looked ill. Temperature 100° F. Moon-faced. Conjunctivæ icteric. Heart slightly enlarged. Liver edge firm and palpable 2 fingerbreadths below the costal margin extending right across epigastrium. Skin: striæ over lower abdomen. Gross muscular wasting of all limbs.

*Investigations.*—E.S.R. 100 mm. in one hour. Hb 68%. W.B.C. 14,600 (polys. 77%). Many L.E. cells present in her blood (confirmed by subsequent tests). Indirect test showed that her serum produced L.E. cell phenomenon in normal white cells of another person. Kahn negative. Serum protein 11·4, albumin 4·2, globulin 7·2 grams per 100 ml. Serum electrophoresis: massive increase in gamma globulin and overall increase of all protein fractions. Serum urea 36 mg. per 100 ml. Urine: Albumin ++.

*Liver function tests.*—Total bilirubin 1·8, direct bilirubin 1·3 mg. per 100 ml. Alkaline phosphatase 13, thymol turbidity 24, zinc turbidity 40 units. Thymol flocculation ++++. Mantoux test 1/1,000 negative. X-ray chest clear. X-ray limbs normal.

*Treatment.*—Prednisone produced marked symptomatic improvement. Limb pains, fever and mild icterus subsided, liver no longer palpable. E.S.R. has become lower, falling to 26 mm. in one hour and L.E. cells have disappeared from her blood. Plasma proteins reduced to 8·8, albumin 4·9, and globulin 3·9 grams per 100 ml., and liver function improved.

# Section of Comparative Medicine

President—J. B. BROOKSBY, D.Sc., Ph.D., M.R.C.V.S.

[*February* 19, 1958]

## Irradiated Helminth Larvæ in Vaccination

By W. F. H. JARRETT, Ph.D., M.R.C.V.S., F. W. JENNINGS, B.Sc., M.Agr., W. I. M. MCINTYRE, Ph.D., M.R.C.V.S., W. MULLIGAN, M.Sc., Ph.D., and G. M. URQUHART, Ph.D., M.R.C.V.S.

*Glasgow*

IN the control of infectious diseases three main methods have been employed, viz. hygienic or public health measures, therapeutic agents and serological preparations. In helminth diseases the first two have been widely used but no efficient method of vaccination, capable of field use, has yet emerged. Yet in certain parasitic infections this type of control is desirable for two reasons: (1) A high percentage of the total pathogenic effect is caused by the migratory stages of the organism and these stages are, in general, not affected by anthelminthics, and (2) modern farm husbandry demands high stock concentrations on pasture and this tends to increase the probability of infection.

Our work on helminth immunity has been concerned mainly with the bovine lungworm *Dictyocaulus viviparus* which migrates through the intestine, mesenteric nodes and lungs, causing lesions there, before reaching its final site in the bronchi and trachea. We have demonstrated that a high degree of immunity is acquired after a suitable infection and that if such immune animals are reinfected twice, then their serum is capable of conferring passive immunity on young susceptible calves (Jarrett *et al.*, 1955, 1957). The degree of immunity throughout these experiments was judged by challenging with a standard number of larvæ and killing the animals in order to count the worms reaching the bronchi. A 50% hæmolysis complement-fixation test was developed (Jarrett *et al.*, 1958*a*) to follow the serological responses.

An attempt was then made to immunize actively calves using a vaccine composed of ground lyophilized whole worm and Freund's adjuvants. Over 100 calves were used in such experiments using a range of methods of challenging and vaccinating procedures and it was found possible to reduce the "take" by about 50% (Jarrett *et al.*, 1958*b*). Although this was promising it was of little value in the field on two counts: (1) Such vaccine is extremely expensive to produce since calves have to be killed to obtain lungworms, and (2) because of the lesions produced. When migrating larvæ or adult worms die in the lungs or bronchi a very severe reaction occurs around them, and, organism for organism, produces much greater damage than takes place in the course of a normal migration. This means, in effect, that a vaccine has to produce a very high degree of immunity so as to prevent the great majority of parasites reaching the lungs or else, in the partially immune animal, a greater degree of pneumonia will be produced than in the completely susceptible calf. A similar pathological sequence has been shown to occur with *Nippostrongylus muris* (Taliaferro and Sarles, 1939).

It was thought that one reason for the failure of dead antigen to produce a high level of immunity was that the response might depend partly on the presence of the metabolic products of living worms. Thorson (1954) has shown this to be the case with *Nippostrongylus* in rats. Therefore we investigated the possibility of attenuating larvæ so that they would reach the mesenteric nodes, exert an antigenic effect and then die so that the pathogenic effects associated with pulmonary migration would not take place. This has been achieved by irradiating the infective larvæ with both X-rays (Jarrett *et al.*, 1957, 1958*c*) and gamma-rays from cobalt 60 (Jarrett *et al.*, 1958*e*). A wide range of irradiating levels was investigated and one such experiment is shown in Table I using 40,000 roentgens and administering 4,000 larvæ to each calf as an oral vaccine. Groups of 10 calves were used. Groups 1a and 2a were killed after thirty days, i.e. when a full adult infection should be established. It is obvious that irradiation had almost wholly prevented an infection in Group 1a, while the expected infection in Group 2a showed that the larvæ used were fully infective. (An approximate dose/infection ratio of 1/4 exists in this disease.) The remaining calves were challenged, together with control Group 3, after sixty days and killed thirty days later. A highly significant immunity was produced in Group 1b, comparable to that produced by a normal severe infection (Group 2b).

TABLE I.—THE IMMUNIZING EFFECT OF IRRADIATED THIRD STAGE LARVÆ

| Group | Treatment Day zero | Mean No. of worms Day 30 | Challenge dose Day 60 | Mean No. of worms Day 90 |
|---|---|---|---|---|
| 1 a | 4,000 larvæ × 40,000 r | 2 | — | |
| 1 b | 4,000 larvæ × 40,000 r | — | 4,000 normal larvæ | 13 |
| 2 a | 4,000 normal larvæ | 906 | — | |
| 2 b | 4,000 normal larvæ | — | 4,000 normal larvæ | 11 |
| 3 | No treatment | — | 4,000 normal larvæ | 1,184 |

Serological studies have shown (Jarrett *et al.*, 1958*a*) that a rise in antibody titre occurs twenty-five days after a first infection and reaches its peak at about one hundred days: on subsequent infections an anamnestic response takes place reaching a peak in seven to fourteen days after infection. When a calf has been vaccinated with irradiated larvæ and is then challenged a rapid secondary response also occurs.

After certain problems of storage, bottlings, &c., had been overcome, it was decided to try such a vaccine under field conditions. This was done in two ways. 15 calves were heavily infected with *D. viviparus* and were allowed to graze on a three-acre pasture. This produced a level of infestation much greater than is normally found under field conditions and represented an extreme challenge to the vaccine. 15 calves were vaccinated with 1,000 irradiated larvæ (i.e. one-quarter of the magnitude of that shown in Table I) and 12 were left as controls: all were then put on to the infected pasture. The detailed results have already been reported (Jarrett *et al.*, 1958*d*) and showed a highly significant difference between controls and vaccinates in respiratory rates, fæcal output of larvæ (and hence further contamination of the pasture) and mortality rates. The results are summarized in Table II.

TABLE II.—THE MEAN GROUP RESPIRATORY RATES, FÆCAL LARVAL OUTPUTS AND MORTALITY OF VACCINATED AND CONTROL CALVES

| Group | Peak respiratory rate per minute | Peak larval output (larvæ/g. fæces) | Deaths | Mortality |
|---|---|---|---|---|
| Vaccinates | 54 | 200 | 3 | 20% |
| Controls | 75 | 700 | 10 | 83% |

The second trial was conducted on forty commercial farms with a past history of parasitic bronchitis. 1,088 calves were included, one-half of those on each farm being vaccinated and one-half left as controls. All calves were fæces-sampled once per month from March until November and their clinical status noted at each visit. The vaccine appeared to be safe under these conditions and no breakdowns in attenuation were found. Parasitic bronchitis broke out on 6 farms and the results (showed in Table III) indicate that a significant degree of protection was achieved.

TABLE III.—RESULTS OF FIELD TRIAL OF VACCINE

| Group | No. at risk | No. with clinical disease | Morbidity |
|---|---|---|---|
| Vaccinates | 48 | 3 | 6% |
| Controls | 43 | 27 | 62% |

At the moment a large experiment is in progress to test the effectiveness of double vaccination against a high challenge dose; this type of procedure is only visualized in farms with a history of severe or lethal parasitic bronchitis.

If this vaccine becomes commerically available, it should have the effect, not only of preventing the disease in some measure, but also of progressively diminishing the parasitic burden of the farm.

## REFERENCES

JARRETT, W. F. H., JENNINGS, F. W., MCINTYRE, W. I. M., MULLIGAN, W., and URQUHART, G. M. (1955) *Vet. Rec.*, **67**, 291.
——, ——, ——, ——, —— (1957) *Vet. Rec.*, **69**, 1329.
——, ——, ——, ——, —— (1958*a*, *b*, *c*, *d*, *e*). In press.
TALIAFERRO, W. H., and SARLES, M. P. (1939) *J. infect. Dis.*, **64**, 157.
THORSON, R. E. (1954) *J. Parasit.*, **40**, 300.

JOINT MEETING No. 1

# Section of Comparative Medicine with Section of Pathology

Chairman—J. B. BROOKSBY, D.Sc., Ph.D., M.R.C.V.S.
(President of the Section of Comparative Medicine)

[*April* 16, 1958]

## DISCUSSION ON RECENT ADVANCES IN DEMYELINATING DISEASE

## Experimental Allergic Encephalomyelitis and Its Immunochemistry

By JACK COLOVER, M.D., M.R.C.P.[1]

*Rheumatism Research Unit (M.R.C.), Canadian Red Cross Memorial Hospital, Taplow, Bucks, England*

DURING recent years the concept that demyelination in the central nervous system may occur as the end result of an auto-sensitization process has been gaining ground. The increase in the knowledge of such processes under laboratory conditions has brought this field nearer to other branches of medicine which have been developing in a similar direction.

Experimental allergic encephalomyelitis was discovered by two groups of workers (Morgan, 1946; Kabat *et al.*, 1946) who found that in monkeys injections of an emulsion of central nervous tissue homogenized with the Freund adjuvants, which contain acid-fast bacilli, resulted in the production of an encephalomyelitis with demyelinating lesions of the white matter. The neurological lesions appeared within a few weeks and frequently were fatal. Subsequently other animals were found to be susceptible, such as rabbits, guinea-pigs, dogs, rats and mice. Homologous, heterologous and autologous brain tissues were found to be effective. All the constituents of the emulsion had to be injected simultaneously at the same site, and either single or multiple injections could be used. Typically in guinea-pigs one sees from the thirteenth day onwards lesions showing cellular infiltration of the vein walls (Fig. 1), areas of perivascular demyelination in the cerebral white matter (Fig. 2) and a patchy meningitis.

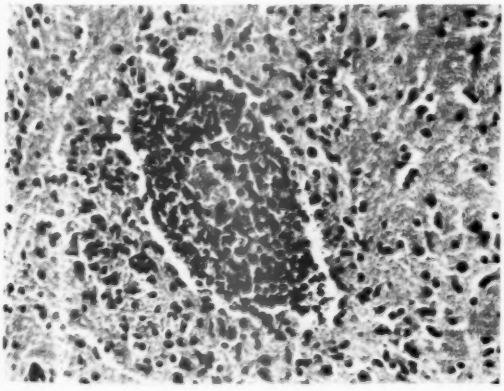


FIG. 1.—Section of guinea-pig brain showing gross cellular infiltration of a vessel wall with surrounding proliferation of microglia in the diencephalon. ×143. (Hæmatoxylin and eosin.)



FIG. 2.—Section of guinea-pig brain showing perivascular demyelination. ×105. (Loyez stain.)

By substituting thyroid gland extracts for the central nervous tissue in the injection material, Rose and Witebsky (1956) found that they could produce thyroiditis in rabbits. This condition was associated with a high titre of circulating antibodies to the thyroid extracts. Similarly Colover and Glynn (1958) by adding homologous adrenal gland to modified Freund adjuvants were able to produce adrenalitis in guinea-pigs. Prior to this Waksman and Adams (1955, 1956) produced an allergic neuritis in various animals by incorporating peripheral nerve

[1] Assisted by a grant from the Medical Research Council.

tissue into the injected emulsion instead of brain or spinal cord. They stressed the importance of species differences in this condition. Thus in the rabbit the lesions occurred mainly in the sensory root ganglia, whereas in the guinea-pig the nerve trunks were mainly affected. Unlike the encephalitis, in none of these conditions were structural changes seen in the blood vessels, which would support the view that the parenchymal damage was not merely the result of mechanical obstruction of the blood vessels.

Species differences have also been noted in allergic encephalomyelitis. Thus in monkeys, hæmorrhages, necrosis, and large areas of demyelination occur. In rabbits on the other hand (Waksman) necrosis is only seen very occasionally, and the location of the lesions is mainly spinal. In contrast to this in guinea-pigs cerebral lesions are very common and with the exception mentioned later, necrosis does not occur. Because of these species differences it may be very difficult to equate the disease in one species with another. In spite of this the view has been put forward that its human equivalent is post-infectious encephalitis. However, as a result of the work of Uchimura and Shiraki (1957) it is believed that the human equivalent is post-rabies-vaccination encephalomyelitis. This condition occurs in some subjects after repeated injection of an emulsion containing attenuated rabies virus in spinal cord. Histologically it occupies a position intermediate between post-infectious encephalitis and disseminated sclerosis, in my opinion.

*Substances Capable of Provoking Allergic Encephalomyelitis*

*C.N.S. fractions.*—It is obvious that further knowledge about the substances responsible for the development of allergic encephalomyelitis might help in understanding its fundamental nature. Lumsden (1949) found that acetone extraction of brain tissue did not destroy its activity. Using bovine spinal cord, treated in this way, as a starting material, Roboz extracted 2 fractions, both of which are active in guinea-pigs. The first (Kies, Roboz and Alvord, 1956) was obtained by autoclaving and behaves as a single substance on paper electrophoresis. Chemically it is similar to collagen or gelatin, and has a hydroxyproline content of over 12%. Because of this it has been called the collagen-like substance. Colover (1957*b*, 1957*c*, 1958) has found a single injection containing 0.2 mg. of this material is effective in guinea-pigs and thus confirmed its activity. The second fraction prepared by Dr. Roboz was extracted with 5% KCl and although it is not a pure substance is more active than the collagen-like fraction. As little as ·004 mg. induced a 50% morbidity index in guinea-pigs (Kies, Roboz and Alvord, 1957). Colover (1957*c*, 1958) has also found this material active. The proteo-lipid obtained by Folch and Lees (1951; Folch *et al.*, 1957) by extraction of bovine spinal cord with a mixture of chloroform and ethanol is active in rabbits and mice, but not in guinea-pigs. Lipton (1957) has obtained a lipid fraction active in guinea-pigs by extracting bovine spinal cord with petroleum ether.

*Bacillary fractions.*—Using intramuscular injections, Colover (1954) found that a crude residue left after extraction of heat-killed human tubercle bacilli with acetone and isopropyl ether was still active. Similar results had been found independently by Allagranza and Rovescalli (1954). Further work on this crude active residue (Colover and Consden, 1955, 1956, 1957; Colover, 1956, 1957*a*) showed that it could be treated with acid, alkali, proteolytic enzymes, and further fat solvents and that the purified residue thus obtained was still quite active. Using another method of injection it was found by White *et al.* (1957), White and Marshall (1958), and by Colover (1957*c*, 1958) independently that a wax material, Wax D Canetti prepared by Dr. J. Asselineau and supplied by Dr. E. Lederer, could induce allergic encephalitis in guinea-pigs. In this method a single injection of 0·2 ml. of an emulsion containing 0·085 ml. Bayol F, 0·015 ml. Arlacel A, 0·1 ml. saline, 1 mg. bacillary fraction and 16 mg. unheated homologous wet brain emulsion, was injected subcutaneously in the dorsum of the hind-foot. By the previous technique Wax D Canetti had only given an occasional positive result (Colover, 1957*b*, 1958).

The purified residue was found to be composed of about 70% protein or peptide, 12% polysaccharide, and about 10% mycolic acid. The principal amino acids in the protein or peptide fraction were glutamic acid, alanine and diaminopimelic acid. The polysaccharide was mainly composed of glucose and galactose (Colover and Consden, 1956). The Wax D Canetti was composed (E. Lederer) of about 50% mycolic acid, 45% polysaccharide and about 5% of peptide made up of 3 amino acids, glutamic acid, alanine and diaminopimelic acid. Thus both the active fractions contain similar amino acids as well as mycolic acid, but the sugars making up the polysaccharide moieties of Wax D Canetti and the active residue are apparently different. Recently a sample of chromatographically pure Wax D Canetti kindly supplied by Dr. Lederer has been found to be active by the method detailed above. This is the first pure chemically defined bacillary agent which has been found to be active. Using this same method of injection the following substances have been found to be inactive when tried on groups of 6 guinea-pigs: lipopeptide from *Nocardia asteroides*, peptide polysaccharide from Wax D Canetti, mycoloyl-alanyl-glycine (E. Lederer). Methyl

mycolate (E. Lederer) and peptide from *E. megatherium* (R. E. Strange) were negative by the intramuscular technique referred to earlier.

*Results of Combining Purified Bacillary and C.N.S. Fractions*

The activity of the crude residue (Colover, 1954) and the purified residue (Colover and Consden, 1956) was confirmed by Kies *et al.* (1958) who combined it with their bovine spinal cord KCl extract. At the same time Colover (1957*c*, 1958) found that the collagen-like fraction prepared by Dr. Roboz was active together with the purified bacillary residue. Also I found the crude Wax D Canetti gave positive results with both spinal cord fractions. More recently it has been found that chromatographically pure Wax D Canetti (1 mg.) combined with electrophoretically pure collagen-like substance (0·2 mg.) induced allergic encephalitis in 4 out of 6 guinea-pigs, so that it is now evident that this condition has been produced by combining 2 apparently pure chemical substances (Colover, 1958).

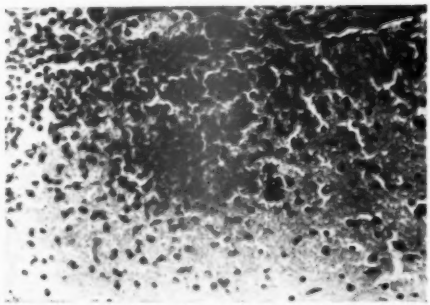


FIG. 3.—Section of guinea-pig brain showing a small necrotic focus under the ependyma. This focus is infiltrated with polymorphonuclear leucocytes and microglial cells and histologically is quite distinct from the reaction shown in Fig. 1. ×350. (Hæmatoxylin and eosin.)

*Variations in Histological Lesions*

There is some evidence that different histological lesions may be produced by differences in the injection materials. Thus when crude Wax D Canetti was injected together with unheated brain emulsion in about half the animals showing encephalitis a new type of lesion which had not been previously recognized in guinea-pigs was seen. It developed at the same time as the other lesions but was characterized by intense infiltration with polymorphs and microglia and small areas of necrosis (Fig. 3).

*Immunological Findings*

The investigation of the immunological aspects of this condition is still in its infancy. At present the only positive finding has been a positive skin reaction to an intradermal injection of 0·1 ml. of 1:100 solution of whole bovine spinal cord KCl extract made by Dr. Roboz in animals which have had this material together with adjuvants. At forty-eight hours the skin at the injection site showed erythema, œdema and occasional necrosis. This suggests that one may be dealing with the delayed type of sensitization to central nervous tissue. However, further work is required on this subject. The mechanism by which the bacillary fraction enables the animal to produce an immune reaction directed against its own tissues provides an exciting field for future study. It is certain that this subject would repay further immunological investigation and in view of the possible species differences which may be present, such an investigation should include human cases of demyelinating disease.

## REFERENCES


ALLAGRANZA, A., and ROVESCALLI, A. (1954) *Boll. Ist. sieroter. Milano*, **33**, 1.

COLOVER, J. (1954) *Brain*, **77**, 435; (1956) *Proc. R. Soc. Med.*, **49**, 154; (1957*a*) *Postgrad. med. J.*, **33**, 115; (1957*b*) *Excerpta med., Amst.*, Section VIII, **10**, Suppl. p. 19; (1957*c*) Proc. Symp. on Experimental Allergic Encephalomyelitis, Oct. 19–20, 1957. Springfield, Ill. In press; (1958) *Nature, Lond.*, **182**, 105.

—— and CONSDEN, R. (1955) *Excerpta med., Amst.*, Sect. VIII, **8**, 808; (1956) *Nature, Lond.*, **177**, 749; (1957) *II Int. Congr. Neuropath.*, 1955, p. 217.

——, and GLYNN, L. E. (1958) *Immunology*, **1**, 172.

FOLCH, J., and LEES, M. (1951) *J. biol. Chem.*, **191**, 807.

——, ——, and STANLEY, G. H. S. (1957) *J. biol. Chem.*, **226**, 497.

KABAT, E. A., WOLF, A., and BEZER, A. E. (1946) *Science*, **104**, 362.

KIES, M. W., ROBOZ, E., and ALVORD, E. C. (1956) *Fed. Proc.*, **15**, 938.

——, ——, —— (1957) *Fed. Proc.*, **16**, 876.

——, ——, —— (1958) *Nature, Lond.*, **182**, 104.

LEDERER, E. (1956) Personal communication.

LIPTON, M. (1957) Remarks in Symposium (*see* COLOVER (1957*c*) above).

LUMSDEN, C. E. (1949) *Brain*, **72**, 517.

MORGAN, I. M. (1946) *J. Bact.*, **51**, 614.

ROSE, N. R., and WITEBSKY, E. (1956) *J. Immunol.*, **76**, 417.

TSUCHIMURA, I., and SHIRAKI, H. (1957) *J. Neuropath.*, **16**, 139.

WAKSMAN, B. H., and ADAMS, R. D. (1955) *J. exp. Med.*, **102**, 213; (1956) *J. Neuropath.*, **15**, 293.

WHITE, R. G., BERNSTOCK, L., JOHNS, R. G., and LEDERER, E. (1957) Personal communication.

——, and MARSHALL, A. H. E. (1958) *Immunology*, **1**, 111.

# Recent Advances in Swayback

By R. M. Barlow, B.Sc., M.R.C.V.S.
*Edinburgh*

The title "Recent Advances in Swayback" is perhaps misleading, implying work carried to a stage when definite conclusions may be drawn. This paper is an interim report of work in progress and any conclusions must be considered more in the nature of suggestions.

The investigation has entailed co-operation between clinician, biochemist, pathologist, and soil chemist and so I propose to give a general statement on swayback, followed by an account of our own findings with emphasis on the clinical and pathological features.

Though swayback has been known for well over a century no description appeared until 1917 when Gaiger mentioned it in an account of "Renguera" a similar disease occurring in Peru. Since 1932 an extensive bibliography has developed and swayback or very closely related conditions are recognized in many parts of the world (Stewart, 1932; Bull *et al.*, 1938; Bennetts, 1932; Bennetts and Beck, 1942; McDonald, 1942; Tabusso, 1942; Innes and Shearer, 1940; Palsson and Grimsson, 1953; Schulz *et al.*, 1951; Dandemaev and Abramova, 1956; Spais, 1956; Gracey and Todd, 1958). A comprehensive review has been recently published by Innes and Saunders (1957).

*Clinical features.*—Swayback is a condition affecting the lambs of apparently healthy ewes of all breeds, at birth or during the first few weeks of life. It is an afebrile, ataxic disease which may be progressive and fatal in all but the most mildly affected cases, and these may accommodate themselves to show almost complete recovery and may in turn give birth to healthy offspring. Ewes may give birth to healthy or affected lambs in successive years.

The most severely affected are stillborn, or weak at birth, may be unable to rise and suckle, and die within twelve to twenty-four hours. If bottle-fed they may survive for long periods. Less severely affected lambs will suckle naturally, but they walk with a staggering, spastic type of gait, often collapsing. The bleat is normal but they may be blind. The ataxia is most noticeable in the hind-limbs but sometimes also affects the fore-legs, and the degree of inco-ordination increases greatly with exercise or excitement. Death in these cases is often the result of secondary infections. Single lambs, or one or more siblings of a multiple birth, may be affected and to different degrees.

*Pathology.*—Innes and Shearer (1940) suggested that the condition was an antenatal, bilaterally symmetrical demyelination of the cerebrum with consequent destruction of the axis cylinders and later cavitation, together with secondary degeneration of the motor pathways. They compared it with Schilder's disease in man. The few pathological studies carried out since 1940 agree in general with these findings and such differences as there are will be discussed later.

*Ætiology.*—Early attempts to incriminate an infectious agent met with no success, and it was not until the mid-1930s that Bennetts and Beck (1942) in Australia proved that the disease was associated with copper deficiency and could be prevented by administering copper supplements to pregnant ewes. His results were confirmed in this country by Dunlop *et al.* (1939). An important ætiological difference, however, between the disease in Australia and Britain is that in Australia the condition occurs on pastures low in copper, i.e. below 5 p.p.m.[1] D.M.[2] and frequently below 3 p.p.m., whereas in this country it occurs irrespective of copper content of the pasture and is prevalent in Derbyshire on pastures containing 7–15 p.p.m. copper or more (Allcroft, 1952). Thus it appears that some conditioning factor may be involved which reduces the availability of copper to the animal (Green, 1951), or causes its increased elimination.

In cattle such a conditioned copper deficiency syndrome occurs on the teart pastures of Somerset, in which copper storage by the liver is reduced due to high dietary molybdenum (Ferguson *et al.*, 1943; Dick and Bull, 1945; Cunningham, 1949). There are, however, no records of swayback occurring on teart pastures, and an experimental attempt to produce the condition by feeding ammonium molybdate and sodium sulphate to pregnant sheep failed, though a degree of hypocuprosis associated with wool dystrophy and hypochromotrichia, was obtained (Wynne and McClymont, 1956). Further, there are local areas in Westmorland where copper deficiency occurs in sheep, associated with wool dystrophy and wasting, in which swayback has not been known to occur (Heath, 1958). These observations suggest that another factor operating in the presence of a low copper status may be necessary for swayback to develop. Antenatal plumbism has also been considered as a factor in the causation of swayback (Bennetts, 1935) but experimental support is lacking.

Thus although copper supplements provide a useful practical answer to the swayback problem little is known regarding the causal factors. The very variable annual incidence which reaches serious proportions on some farms in some years still makes the disease of considerable importance to the individual farmer, although on a national scale it is of small

[1]Parts per million. [2]Dry Matter.

consequence. Its importance in the field of comparative medicine need not be stressed. In this connexion there is the report of Campbell *et al.* (1947) on seven swayback research workers, four of whom developed disorders of the nervous system clinically indistinguishable from disseminated sclerosis.

*The work in Edinburgh.*—In the spring of 1956 a hill flock was encountered in which over 20% of the lamb crop had been lost as the result of an ataxic condition. An account of the clinical features and pathology has already been published (Barlow, 1956). At the time of examination all the remaining lambs were over a month old; the history and clinical signs suggested swayback, but in no case was it possible to demonstrate cerebral demyelination. The predominant lesion was a hyaline necrosis of multipolar nerve cells scattered throughout the nuclei of the brain-stem and ventral horns of the cord; though numerically insufficient it seemed to account for the clinical signs. The livers of the few lambs examined biochemically were found to have low copper values.

Accordingly it was resolved in collaboration with Dr. E. J. Butler of Moredun Institute and Dr. D. Purves of the East of Scotland College of Agriculture to study this farm throughout the season 1956–57. The two adjacent farms, one of which had a similar history of ataxia, the other being alleged free, were also included for detailed observation. A controlled dosing experiment was carried out on one of these farms. In addition, during the 1957 lambing season another score of affected farms within the College area were visited, as detailed a history as possible taken, suspected cases examined clinically and material obtained for biochemical and pathological examination, and pasture for trace element analysis. Much of the information obtained has yet to be correlated and its significance assessed but it is hoped to publish a detailed report in due course. The following is a brief account of our findings so far.

More than 75% of the outbreaks occurred on marginal or hill farms lying chiefly between the 500–1,500-feet contours, the sheep having a run-off to variable amounts of ploughed land. With few exceptions the disease occurred on land which had been heavily and repeatedly limed. Most of the farms had a previous history of sporadic cases or small outbreaks but in 1957 there was an overall increase in incidence, losses varying from 2–25% of the lamb crop. The condition was seen in Blackfaces, Border Leicesters, Cheviots, and Suffolks, and their various crosses, but most commonly in Border Leicester × Blackface (Greyface) lambs.

The most severe cases were stillborn or very weak at birth and failed to rise and suckle the ewe and unless bottle-fed died very soon. Others could get to their feet and suck naturally but showed the typical ataxia which became more pronounced with exercise or excitement. Fresh mild cases were noticed until the lambs were 8–10 weeks old.

In no case was there clinical evidence of hypocuprosis or other disease in the ewes.

Soil and pasture from suspect areas were collected by a method designed to give representative samples (Calder and Voss, 1957), and analysed spectrographically for a wide range of trace elements. With respect to copper, the herbage values obtained from 46 fields varied from 1·8–25·5 p.p.m. dry matter. The average was 5·9 p.p.m. and the standard deviation was roughly within the normal range for pasture in England and Wales reported by Eden (1944).

*Biochemical findings.*—Blood samples were taken from ewes giving birth to affected lambs on all the farms visited, and the copper levels determined. In addition the livers of all lambs taken for pathological examination were analysed, and in some cases the blood copper values of these lambs were also determined.

It was found that the mothers of swayback lambs had unusually low blood copper values, i.e. 60 $\mu$g./100 ml. and in some cases down to $<1{\cdot}0$ $\mu$g./100 ml. Affected lambs were also found to have unusually low blood and liver copper. A close correlation between the degree of hypocuprosis at the time of sampling and the severity of the lesions at post-mortem was not apparent, though these data have yet to be analysed statistically.

*Dosing experiment.*—The flock examined in 1956 was divided into two groups of about 100 ewes and 50 ewes respectively. The larger group was dosed with 1·0 gram of $CuSO_4$ *per os* three times, at monthly intervals, during pregnancy, the last dose being given about ten days before lambing was due to commence. The other group was kept as a control. Blood copper levels of individual animals in both groups were determined at monthly intervals. Further blood samples were taken from the adjacent farm which had no history of swayback.

Whilst very great differences in blood copper levels between individual sheep on both farms were found, the majority were below 60 $\mu$g./100 ml., i.e. within the range where swayback is likely to occur (Allcroft, 1952). The administration of copper sulphate produced no significant alteration in the blood copper levels when sampled one month after dosing. Subsequently it was found that the dosed group showed a 3% incidence of swayback whilst in the control group it was about 23%. Some ewes giving birth to normal lambs had, in fact, significantly lower blood copper values than those with affected lambs. The adjacent farm

which was similar in respect to geographical and climatic conditions, but where no liming or other attempts to improve the pasture had been made, had no cases of swayback, though the blood copper values of the ewes were within the swayback range. These findings bear out other authors' conclusions of a "one-way correlation" between low copper status and swayback (Allcroft, 1952).

*Pathology.*—With only a few exceptions the lambs for pathological examination were freshly killed by a standard method, the central nervous system removed to fixative as soon as possible and the subsequent treatment of tissues was by standardised techniques throughout. A total of 47 lambs representing all ages from birth to 10 months old and all degrees of clinical involvement was examined.

The macroscopic cerebral lesions of cavitation or gelatinization described by Innes and Shearer (1940) were only observed in 38% of cases, as compared with 70% in their series of 167 cases. Unless hand-fed no lamb showing these lesions was more than 2 weeks old. On the other hand, equivalent clinical cases without gross cerebral lesions were found throughout the series. Some cases showed slight dilatation of the lateral ventricles and reduction in size of the diencephalon in the region of the anterior cerebral commissure.

Lesions were not observed in other organs apart from unilateral gluteal atrophy in one older case (9 months) and periglomerular fibrosis with tuft atrophy and hypertrophy of the lining epithelium of Bowman's capsule in the kidneys of a few cases aged 4–5 weeks. Similar renal lesions have been observed in other conditions of lambs (Butler *et al.*, 1957; Hartley, 1953).

*Histology of the Central Nervous System*

*Cerebrum.*—Even in the motor area cortical changes were few and consisted of dilatation of the perivascular spaces and occasional fine stippling of the cytoplasm of nerve cells with shrinkage and pericellular œdema.

The white matter of the hemispheres showed lesions varying from gross fluid-filled cavities to tiny foci of gelatinous appearance at the tips of the gyri or in the *centrum ovale.* The cavities were bounded by a feltwork of fibrous glia having the appearance of a compression capsule whilst the gelatinous areas consisted of a loose glial network containing few axis cylinders or myelin sheaths. Intense glial proliferation has not been seen, no inflammatory reaction observed, and in all but 2 recent cases fat phagocytes have been remarkably few in number; findings which are in close agreement with those of Innes and Shearer (1940). In 2 cases, however, masses of gitter cells have been present around the lesions extending into the adjacent cortex along the vessels. Using Spielmeyer and Marchi techniques, normal myelin appeared to extend up to the edge of the lesions.

In 62% of cases, however, no lesions of cerebral myelin could be detected, which compares with the findings of McDonald (1942).

*Cerebellum.*—No lesions were observed apart from a few Marchi-positive fibres in the *corpus medullare* of the youngest animals.

*Brain-stem and cord.*—In 97·5% of all cases under 12 weeks old chromatolytic changes extending to a hyaline-like necrosis were found in varying numbers of the large neurons of the stem and ventral horns of the cord, and using Holmes' (1947) technique the neurofibrillary apparatus would appear to be damaged in a larger proportion. The number and situation of affected cells varied from case to case. Cell changes have been mentioned by Stewart (1932), Innes and Shearer (1940), McDonald (1942), Dandemaev and Abramova (1956).

In the younger cases Marchi-positive fibres have been seen running through the brain-stem to become localized in the dorsolateral and sulcomarginal funiculi of the cord. Smaller concentrations were also seen in the septomarginal funiculi. In no case has sclerosis of the cord (McDonald, 1942) been observed.

*Sciatic nerves.*—A few Marchi-positive fibres have occasionally been seen in the sciatic nerves.

*Normal animals.*—A small series of normal animals has been examined by the same standardized methods. In those under 10 days old Marchi-positive material has been found in the same sites as in swayback lambs. In addition similar quantities of sudanophilic material were present between nerve fibres and in the perivascular spaces.

Examination of material prepared by a bulk fixation technique has indicated that some of the Marchi-positive material may be, in fact, stretch artifact (Smith, 1951, 1956).

A preliminary histological examination of fœtal nervous tissue has revealed a picture somewhat similar to that seen in some cases of swayback. The cortical neurons show fine stippling of the cytoplasm and lie in "retraction spaces" and areas of active medullation have the appearance of the gelatinous lesions of the disease, similar quantities of sudanophilic material being present. Further work, however, is required to determine how far this similarity exists.

## Discussion

Our clinical, chemical and biochemical observations bear out those of previous workers to a large extent and identify the condition we are studying with that previously described.

In our experimental group of farms the one on which no cases of swayback occurred was adjacent to the one showing a 23% incidence in the untreated group. The geographical and climatic conditions were similar on both farms, and comparable copper values were found in both pasture and sheep. On the farm with the disease, however, a more intensive flock and pasture management was practised which included heavy repeated liming over a period of years. It would appear that some factor associated with this type of management may be involved in the causation of swayback.

The definitive cerebral lesions were observed in only 38% of our cases as compared with 70% in Innes' series. It was not possible to predict clinically the presence or absence of these lesions in animals less than 2 weeks old and thus one is inclined to doubt that they constitute the significant lesions of the disease.

The presence of necrotic neurons in 97·5% of our cases, on the face of it, appears to be much more significant. In many instances, however, these are not numerous and even taking into account the less severe chromatolytic changes in other nerve cells, the total number of cells involved frequently does not appear to be sufficient to account for the clinical condition of the animal. It is tempting to postulate the presence of an extensive functional lesion of neurons not visible by the methods so far employed. In this connexion mitochondria and Golgi apparatus may be worthy of attention.

In spite of the varying degree of cerebral involvement, the extent of the so-called "secondary tract degenerations" appeared remarkably constant and did not seem to be related to the numbers of abnormal multipolar nerve cells observed in the brain-stem. It thus seemed likely that some of this Marchi-positive material was artifact. If so, the constancy of distribution at all levels of the cord suggested that it might be the result of stretching of unfixed fibres.

The study of the central nervous system of normal lambs of equivalent ages by the same standard techniques showed a similar distribution of Marchi-positive fibres. Bulk fixation methods designed to avoid stretching of unfixed fibres may reduce this to some extent.

This modified treatment of tissues has still to be applied to swayback material but in the light of these findings it seems likely that some difficulty may be experienced in interpreting the results.

The relatively small amounts of intra- and extra-cellular lipoid present around the cerebral lesion in the great majority of cases have been considered as evidence of a demyelinating process. That similar amounts are present in animals showing no lesions, in normal young animals and also in fœtuses where medullation is occurring lends support to the theory that the cerebral lesion is due to myelin aplasia rather than demyelination. This theory was advanced by Innes and discarded as untenable on the grounds that in swayback the "... brain as a whole is a well-developed full-time organ in respect of size, conformity and structure ..." and because " ... it would not explain the porous areas, the gross cavitation, nor the myelin destruction demonstrated by positive staining reactions (Marchi or Scharlach R methods). ..."

Further support for an aplasia or dysplasia theory may become apparent from a closer study of the fœtal cerebrum prior to the completion of medullation, in relation to the swayback brain showing the gelatinous lesion. Superficially they appear to show some similarity.

## Conclusions

(1) Whilst the clinical picture of swayback is fairly characteristic, variations in the pathological manifestations have been observed.

(2) Though diagnostic when present, the inconstancy of the cerebral lesion, and its absence in some of the more severe cases, suggests that the fundamental lesion may be elsewhere.

(3) The interpretation of Marchi preparations of the spinal cord taken by routine methods should be treated with reserve.

(4) The presence of necrotic neurons is a useful aid to diagnosis. The suggestion of more widespread cellular changes indicates the need for further work.

(5) Similarities between normal fœtal and swayback brains have been observed which would support the theory of myelin aplasia or dysplasia, if substantiated.

## References


ALLCROFT, R. (1952) *Vet. Rec.*, **64**, 17.

BARLOW, R. M. (1956) *Vet. Rec.*, **68**, 712.

BENNETTS, H. W. (1932) *Aust. vet. J.*, **8**, 137 and 183.

—— (1935) *J. Coun. sci. industr. Res., Aust.*, **8**, 61.

——, and BECK, A. B. (1942) *Bull. Coun. sci. industr. Res., Aust.*, No. 147.

BULL, L. B., MARSTON, H. P., MURRANE, D., and LINES, W. E. L. (1938) *Bull. Coun. sci. industr. Res., Aust.*, No. 113, p. 23.

BUTLER, E. J., NISBET, D. I., and ROBERTSON, J. M. (1957) *J. comp. Path.*, **67**, 378.

CALDER, A. B., and VOSS, R. C. (1957) *Consultative Committee for the Development of Spec graphic Work. Bulletin* 1.
CAMPBELL, A. M. G., DANIEL, P., PORTER, R. J., RUSSELL, W. R., SMITH, H. V., and INNES, J. R. M. (1947) *Brain*, **70**, 50.
CUNNINGHAM, I. J. (1949) *XIV Int. Vet. Congr.*, **3**, 48.
DANDEMAEV, S. G., and ABRAMOVA, S. M. (1956) *Veterinariya Moscow*, **33**, 38.
DICK, A. T., and BULL, L. S. (1945) *Aust. vet. J.*, **21**, 70.
DUNLOP, C., INNES, J. R. M., SHEARER, G. D., and WELLS, M. (1939) *J. comp. Path.*, **52**, 259.
EDEN, A. (1944) *J. comp. Path.*, **54**, 220.
FERGUSON, W. S., LEWIS, A. M., and WATSON, S. J. (1943) *J. agric. Sci.*, **33**, 44.
GAIGER, S. H. (1917) *J. comp. Path.*, **30**, 185.
GRACEY, J. F., and TODD, J. R. (1958) *Vet. Rec.*, **70**, 238.
GREEN, H. H. (1951) *J. R. agric. Soc.*, **112**, 36.
HARTLEY, W. J. (1953) *N.Z. Vet. J.*, **3**, 63.
HEATH, G. B. S. (1958) Personal communication.
HOLMES, W. (1947) In: Recent Advances in Clinical Pathology. Edited by S. C. Dykes. London; p. 402.
INNES, J. R. M., and SAUNDERS, L. E. (1957) Recent Advances in Veterinary Sciences. Edited by C. A. Brandly and E. L. Jungherr. New York; **3**, 67.
——, and SHEARER, G. D. (1940) *J. comp. Path.*, **53**, 1.
MCDONALD, I. W. (1942) *Aust. vet. J.*, **18**, 165.
PALSSON, D. A., and GRIMSSON, H. (1953) *Proc. Soc. exp. Biol. N.Y.*, **83**, 518.
SCHULZ, K. C. A., VAN DER MERWE, P. K., VAN RENSBERG, P. J. J., and SWART, J. S. (1951) *Onderstepoort J. vet. Res.*, **25**, 35.
SMITH, M. C. (1951) *J. Neurol. Psychiat.*, **14**, 222.
—— (1956) *J. Neurol. Psychiat.*, **19**, 62, 67, 74.
SPAIS, A. G. (1956) Enzootic Ataxia of Lambs in Greece. The University, Thessalonika. (In Greek.)
STEWART, W. L. (1932) *Vet. J.*, **88**, 35.
TABUSSO, M. E. (1942) *Publ. Inst. nacl. Biol. Anim. Lima*, **1**, 91.
WYNNE, K. N., and MCCLYMONT, G. L. (1956) *Aust. J. agric. Res.*, **7**, 45.

## Demyelinating Disease: The Present Situation

By Professor C. E. LUMSDEN, M.D.
*University of Leeds*

MULTIPLE sclerosis is now too urgent a problem for temporizing approaches. In this disease too many leads have remained unfollowed; too many answerable questions have evoked no enquiry.

Since relation between "swayback" and human disease is implied in this discussion, I shall begin by referring to the report of Campbell *et al.* (1947) which has naturally received prominence in the world literature on demyelinating disease. It will be remembered that four out of seven research workers on swayback were thought to be affected by a disease indistinguishable from multiple sclerosis. Since over ten years have now elapsed, ample time would seem to have occurred for re-assessment of this report. In this instance some fresh information would seem to be a paramount scientific need. The clinically most typical case of the four was the only one known to me; this patient eventually succumbed to multiple sclerosis which—I think by a curious coincidence only—happened to be of a rather "transitional" type with diffuse cerebral demyelination and with plaques of the more typical discrete type only in the optic pathway, cerebellum, brain-stem and cord. I hope to report and illustrate the pathological findings in this case elsewhere in full detail. As far as I can ascertain this case was purely coincidental and has no relevance whatsoever to the swayback problem. If we were to learn that the diagnosis of multiple sclerosis is no longer tenable in the remaining cases cited in the 1947 report I think it would be of real value in the difficult field of multiple sclerosis research.

The suggestion of communicability implicit in the swayback report reminds us that the infection hypothesis is the oldest and still most widely favoured among neuropathologists—a view reiterated by Greenfield *et al.* (1958). The Shubladze vaccine, too, has been the subject of recent lay and medical publicity (1958, *Brit. med. J.*, i, 821). Two facts call for re-emphasis: (1) The Russian E.H.A. virus, strain Sv. ("encéphalomyélite humaine aiguë", from patient Sv.), used for the vaccine, was isolated from a case that would not be diagnosed as multiple sclerosis here (Margulis *et al.*, 1946); and (2) the vaccine is a (rodent) brain suspension and, even though formolized, liable to produce allergic encephalitis in view of what we know of the experimental disease. The virus question is therefore still entirely open. Supporters of a virus ætiology have criticized the earlier negative work on the grounds that a causative virus for multiple sclerosis might be human-specific as well as brain-specific. To investigate this an attempt was made to work out a tissue culture method using human nervous tissue, with neurons, neuroglia and cerebral mesoblastic cells, and taking fresh plaque material under aseptic conditions within the first few hours (Lumsden, 1957*c*). The method came as closely as possible to satisfying technically the most stringent criticisms since it succeeded in

recovering from the plaque tissues still-viable tissue cells which might reasonably be expected to act at least temporarily as vehicles, if not hosts, for the virus until the nerve fibres and neuroglia from the implanted normal tissue had had time to merge with the living cells and dead fragments from the plaque tissue under test (Fig. 1). The results were completely

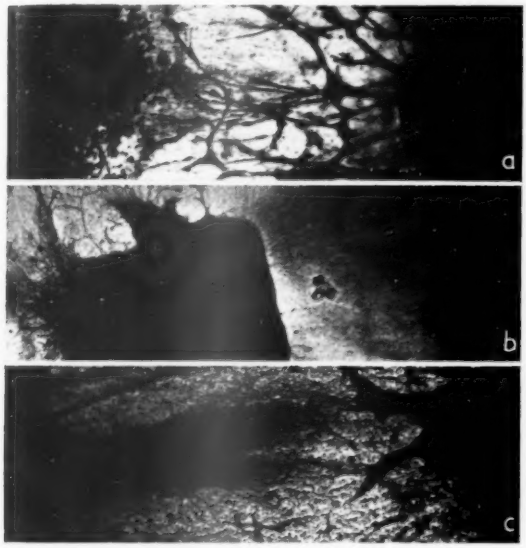



FIG. 1.—Use of cultures of fœtal human brain tissue for test for possible virus in plaque tissue. The cultures of the fœtal tissue are on the left and the implanted plaque tissue on the right. Outgrowth of fœtal glia seen in "a" and "b", and of axons in "b" and "c". The plaque tissue gives rise to mesoblastic cells migrating towards the fœtal brain cultures. Bodian's stain. "a" ×103; "b" ×44; and "c" ×96.

negative in all plaques taken from the six cases of multiple sclerosis tested but are not considered as more than suggestive since no case of really florid "acute multiple sclerosis" was included. In the event of such a case occurring, the brain should be removed aseptically within three or four hours and fragments of 3–4 mm. diameter each, at the edges of fresh plaques, distributed in sterile bijou bottles and stored and transported in solid carbon dioxide—a method by no means ideal but the only practicable one where the culture facilities just outlined are not immediately available.

The foregoing method as carried out on fresh unfrozen tissue in these six cases served also to provide a reasonable method for culturing larger organisms like spirochætes. Steiner (1952) insists that, with careful search *in acute plaques* and by scrupulous attention to technical processing and staining, spirochætes which are neither artifacts nor technical contaminants can be found in early acute lesions which are not found in control material or in older plaques. His long experience and advocacy of an unpopular doctrine against hostility commands serious attention. Using his method I found no stainable spirochætes in selected plaques from the same cases as were used for virus testing. We have also processed a certain amount of material from other cases the examination of which is still incomplete. But the critical condition for adequate refutation of Steiner's doctrine would be failure to find such spirochætes in all cases of fatal "acute multiple sclerosis". These cases should be freshly autopsied and selected plaques cut immediately and fixed in 10% formalin made with freshly distilled water. The processing can be done subsequently in any laboratory of neuropathology which will, no doubt, collaborate in this problem provided that the case is suitably selected and the material taken with stringent care. The microscopical scrutiny of such material is especially exacting and familiarity with such artifacts as those shown in Fig. 2 is necessary. At the same time, darkfield examination of exudate from bedsores, as well as fixation of

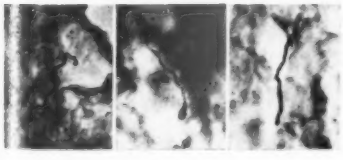


FIG. 2.—Spirochæte-like artifacts seen in brain tissue of case of multiple sclerosis. Brain freshly cut within four hours of death. Tissue fixed in 10% formalin. Stained with Steiner's method. All ×978.

portions for Steiner's method is advisable since the real issue in Steiner's findings is whether the spirochætes in his cases may have been of sapræmic nature in moribund patients with extensive bedsores. In multiple sclerosis out-patient clinics, the recent claims of Ichelson (1957) to have isolated spirochætes from C.S.F. by culture could presumably be tested stringently within, perhaps, a matter of twelve to eighteen months without too great an expense outlay. All these laboratory investigations seem to require to be repeated properly if the spirochæte claims are to be adequately revaluated, since therapeutic trials with antibiotics are likely to be more difficult to assess, for reasons mentioned elsewhere (McAlpine, Compston and Lumsden, 1955).

Experimentally, "allergic" encephalomyelitis is a contribution primarily to general pathology as much as to neurology since it is quantitatively the most striking example of a purely immunopathological process. Unfortunately, until specific antigens or antibodies are identified it is premature to talk of its "immunochemistry" since the refined quantitative methods of immunochemistry have not, and cannot, yet be brought to bear upon it. A relationship between experimental "allergic" ECM and human post-infectious encephalomyelitis has been postulated but there is as yet no scrap of laboratory evidence for this. In Leeds, with Périer and Marmion, I have this year begun to try to get some direct evidence for such a relationship (unpublished experiments). Cavy-passaged vaccinia virus has been used to produce skin vaccinia of different degrees of severity in guinea-pigs. Then, at different time intervals, affected skin has been removed and sterilized variously by autoclaving or by treatment with β-propiolactone or formalin, homogenized with adjuvants and injected (to date) into sixty test animals. This experiment has failed to produce allergic encephalomyelitis.

While efforts have begun to be made elsewhere to purify the components of the injection mass in the hope of isolating pure antigens and, with the use of complement fixation and skin sensitivity methods, to demonstrate the antibodies presumptively involved, next to nothing has been done towards understanding the pathogenesis of the structural lesions. An obvious postulate accounting for the special susceptibility of brain tissue to an immunopathological process is that it is somehow bound up with the blood-brain-barrier and the late development of myelin, resulting in a failure of acquired immunotolerance to myelin lipoprotein (Lumsden, 1957*a*). There is some experimental support for this hypothesis (Paterson and Hansbrote, 1957).

It has been too uncritically accepted that this is a "demyelinating" disease. My personal experience is based on four experimental species—guinea-pig, monkey, goat and rat—and from these as well as from the literature on the disease in other species I am unable to accept that "allergic" ECM is specifically demyelinating. The lesions are primarily vascular and, as illustrated earlier at this Society (Lumsden, 1956), may or may not involve the parenchymatous tissue components. When most of the vessels in an area are affected confluent parenchymatous destruction may result, leading in myelin preparations to a pale area. In so far as axon destruction accompanies the demyelination and a state of spongiosis follows it can be said that some necrosis accompanies all lesions. Distinction between necrotizing and non-necrotizing types of lesions seems to me to be false. Trypan blue studies show extensive perivascular oedema (own observations) so that this factor alone may play an important role in the secondary parenchymatous damage. Also, in view of what is now known of the pharmacology of the inflammatory response it would seem desirable, in this often excessively severe inflammatory process, to investigate whether histamine-like substances and pharmacologically active polypeptides or other "spreading factors" may be released from the mesoblastic cells in the vessel walls which are so profoundly stimulated in this process. Such "spreading factors" might be responsible for some aspects of the parenchymatous damage.

Whatever the pathogenesis of allergic encephalomyelitis, the fact is that no experimental instance has, to my knowledge, been published or illustrated which reproduces specifically demyelinating lesions in any way approaching the characteristic lesions of multiple sclerosis which I think it is important to re-examine regularly if one is to keep one's sense of perspective (Fig. 3). Refuge has been taken by many in the postulate that the difference may be merely a species one: that man with experimental "allergic" ECM would get multiple sclerosis. In fact there is no evidence that human post-infectious ECM proceeds to multiple sclerosis (Lumsden, 1951). Uchimura and Shiraki's (1957) cases, ostensibly of anti-rabic vaccinial ECM, have been cited as bridging the gap between the experimental allergic ECM and human multiple sclerosis on the argument that these multiple sclerosis-like lesions following anti-rabic vaccination have special significance in a country where multiple sclerosis is said to be extremely rare. But if we accept this reasoning then we are confronted with a very disturbing conclusion: viz. that multiple sclerosis can readily enough be reproduced in the brains of natives of Japan provided that an adequate exogenous cause is operative.

All the foregoing lines of investigation need to be carried through to conclusion without delay. It will be obvious, however, that I personally feel, for various reasons considered elsewhere (McAlpine *et al.*, 1955), that their solution will not answer the riddle of multiple

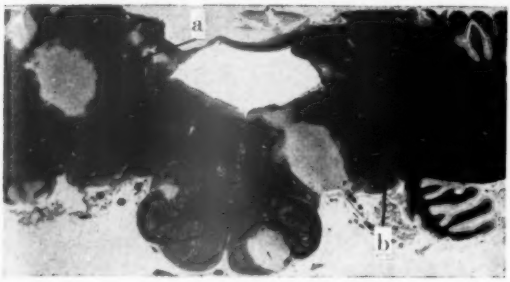



FIG. 3.—Typical plaques in cerebellum and medulla in chronic case of multiple sclerosis. Five completely demyelinated patches with abrupt contours, and "shadow plaques" at "a" and "b". Note the clearly-demarcated "shadow-plaque" haloes of the two largest plaques: also the mode of peripheral extension of the largest plaques and the central vessel in the plaque in one of the pyramids. Stained for myelin. Enlarged.

sclerosis although they will clear the field and will therefore be enormously useful. In the end I feel we will be held up chiefly because we do not yet know enough about the biology of myelin. For instance, chemically there is evidence for a slow but constant metabolic turnover of myelin, and for a slow maturation from childhood to adulthood—the evidence for which has been considered elsewhere (Lumsden, 1957*b*). These suggest at least two fundamental questions of possible immediate relevance to demyelinating disease: (*a*) what do we know of the structural stability of myelin, and (*b*) can sheaths regenerate *in vivo* provided the axoplasm is viable? These two questions, along with a third "Can sheaths be selectively affected *in vitro*?" are the sort of vital questions which I feel that we require urgently to answer and to which we have turned now in our laboratory using the methods of Peterson and Murray and of Hild on tissue culture of avian spinal ganglia and mammalian cerebellum during the time of myelination.

## REFERENCES


CAMPBELL, A. M. G., DANIEL, P., PORTER, R. J., RUSSELL, W. R., SMITH, H. V., and INNES, J. R. M. (1947) *Brain*, **70**, 50.

GREENFIELD, J. G., BLACKWOOD, W., MEYER, A., MCMENEMEY, W. H., and NORMAN, R. M. (1958) Neuropathology. London.

ICHELSON, R. R. (1957) *Proc. Soc. exp. Biol., N.Y.*, **95**, 57.

LUMSDEN, C. E. (1951) *Brit. med. J.*, i, 1035.

—— (1956) *Proc. R. Soc. Med.*, **49**, 148.

—— 1957*a*) *III Congrès Internat. de Neuropathologie:* Acta Medica Belg., Bruxelles; p. 27.

—— (1957*b*) In: Modern Trends in Neurology. Second Series. Edit. D. Williams. London; pp. 130, 148.

—— (1957*c*) *II Int. Congr. Neuropath.*, 1955, p. 429.

MCALPINE, D., COMPSTON, N. D., and LUMSDEN, C. E. (1955) Multiple Sclerosis. Edinburgh.

MARGULIS, M. S., SOLOVIEV, V. D., and SHUBLADZE, A. K. (1946) *J. Neurol. Psychiat.*, **9**, 63.

PATERSON, P. Y., and HANSBROTE, M. I. (1957) *Bact. Proc.*, 88.

STEINER, G. (1952) *J. Neuropath.*, **11**, 343.

UCHIMURA, I., and SHIRAKI, H. (1957) *J. Neuropath.*, **16**, 139.


## DISCUSSION

**Dr. J. Olivier Périer** (Pathology Department, University of Leeds)[1]: *In vitro* formation of myelin in both the peripheral and central nervous systems, as reported respectively by Peterson and Murray (1955) and by Hild (1957), is sufficiently important in itself to warrant confirmation and study, theoretically affording a fairly simple experimental system for morphological and histochemical studies of myelinogenesis. But here we wish only to draw attention to three points which have direct implications for demyelinating diseases:

(1) *The relation of myelin sheath formation to satellite cells.*—Peterson and Murray, using avian spinal ganglia, find that myelination *in vitro* occurs only when the Schwann cells have come into close apposition with the nerve fibres, and serial photography shows that an actual wrapping or winding process is involved (Murray, 1957). In such preparations the axon migrates out first as a non-myelinated fibre unaccompanied by Schwann cells. Subsequently, Schwann cells move into permanent apposition with the fibre. Myelination, however, occurs only sporadically and when it does occur it can be seen that it is *de novo*. On the other hand, with kitten and puppy cerebellum cultures, the myelin (Fig. 1A and B), which can be obtained more easily in our hands than in the Peterson-Murray preparation, occurs apparently in the area of spreading of the explant behind the fringe of migrating mesoblastic and glial cells, and bears no spatial relationship to glial cells. It is thus less clear in these conditions that the axons have migrated and that the myelin is new-formed. Hild concludes from his studies that it is new-formed myelin. We find that when myelin "reappears" after several weeks it

[1] British Council Fellow. Permanent address: Pathology Department, University of Brussels.

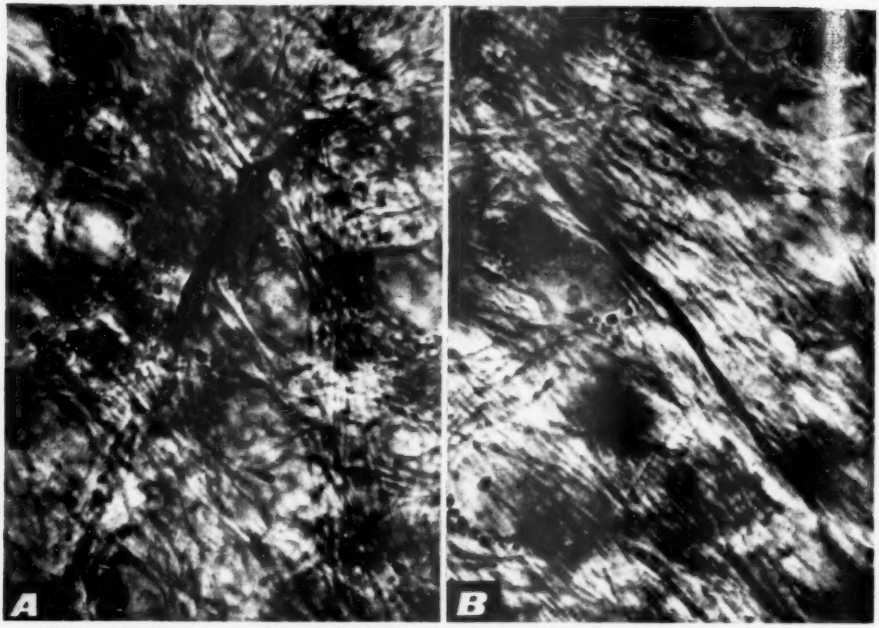



FIG. 1.—Myelin *in vitro*. Two myelinated segments of axons after forty days *in vitro* from a culture of a fragment of cerebellar folium of a 10-day-old kitten. In zone of neuroglial spread. The background fibres are mainly neuroglial but include many non-myelinated axons. Fixation by formol-Ringer. Stained with Sudan black B. ×1,300.

N.B.: In "A" the fibre shows a fusiform swelling of the myelin in the centre of which the axon can be seen.

sometimes does so with such rapidity and so profusely distributed that it seems impossible that it can be pre-existing myelin which has been missed before.

(2) *Selective demyelination* in vitro.—Both in the Hild material and in the Peterson-Murray preparations with older embryos, many nerve fibres are already myelinated *in vivo* at the time of explantation. If these authors' findings are accepted then the possibility exists that in the conditions of culture, demyelination with axon survival and subsequent remyelination may be occurring. Since both of these possibilities are of such importance to the problem of multiple sclerosis, direct observational evidence on individual fibres will be necessary. While it seems beyond question that new myelin is formed in Peterson and Murray's cultures, the original state of the axons—whether they were originally myelinated or non-myelinated—still calls for demonstration. In the Hild type of preparation we have not yet been able to decide whether the individual fibres that form myelin *in vitro* were originally non-myelinated, or whether they were myelinated fibres which lost their myelin at first *in vitro* and re-formed it later.

(3) *Persistence of myelin* in vitro.—In some parallel studies on human adult sympathetic ganglia, non-growing but still myelinated fibres *can* be observed projecting from the frayed edges of the explants. For as long as six weeks after explantation, myelin sheaths have been seen to retain their morphological characteristics including a strong birefringence. These nerve fibres never developed any signs of growth nor of any movements at the tips of their processes and so were evidently dead. Furthermore, being myelinated, they were presumptively pre-ganglionic and must therefore have been severed from their neurons of origin at the time of explanting. The only conclusion seems to be that with these more mature fibres in the conditions of culture the process of myelin breakdown is retarded or arrested compared with the normal situation *in vivo*. We are hoping this may afford us the opportunity of studying the stages of myelin degradation *in vitro*.

## REFERENCES

HILD, W. (1957) *Z. Zellforsch.*, **46**, 71.
MURRAY, M. R. (1957) IX Internat. Congress for Cell Biology. St. Andrews. (Demonstration.)
PETERSON, E. R., and MURRAY, M. R. (1955) *Amer. J. Anat.*, **96**, 319.

# Section of Pathology

President—Professor J. W. S. BLACKLOCK, M.D.

[*March* 18, 1958]

## Folic Acid Deficiency and the Megaloblastic Anæmias

By I. CHANARIN,[1] M.D., D.C.P., D. L. MOLLIN,[2] M.B., and B. B. ANDERSON, B.Sc.
*London*

MEGALOBLASTIC anæmia is the consequence of deficiency or interference with utilization of vitamin $B_{12}$ or folic acid. The ætiology of those megaloblastic anæmias which respond completely to treatment with vitamin $B_{12}$ is fairly simple: it is due to deficiency of vitamin $B_{12}$ and this is almost invariably due to a failure of its absorption; rarely to an inadequate dietary intake. The megaloblastic anæmias which we shall discuss do not respond adequately to vitamin $B_{12}$, and folic acid is required in their treatment.

The conditions with which these megaloblastic anæmias have been associated are shown in Table I. Of these, only two occur with any degree of frequency in temperate climates,

TABLE I.—MEGALOBLASTIC ANÆMIA WHICH REQUIRES TREATMENT WITH FOLIC ACID OCCURS IN

1. Idiopathic steatorrhœa
2. Pregnancy
3. Anticonvulsant treatment of epilepsy
4. Leukæmia and related disorders
5. Cirrhosis
6. Tropical sprue
7. Nutritional megaloblastic anæmia
8. Kwashiorkor

namely the megaloblastic anæmia of pregnancy and the megaloblastic anæmia associated with idiopathic steatorrhœa. Megaloblastic anæmia requiring folic acid is far more common in tropical and semi-tropical countries, and again is often associated with pregnancy and with sprue.

The study of vitamin $B_{12}$ in this connexion has been simplified by the introduction of two techniques. The first is a method for the assay of the vitamin $B_{12}$ content of serum as a result of which $B_{12}$ deficiency could be assessed (Ross, 1950; Rosenthal and Sarett, 1952; Mollin and Ross, 1952); the second is the introduction of methods for the study of the absorption of vitamin $B_{12}$ (Heinle *et al.*, 1952).

The purpose of this paper is to describe methods serving a similar function in relation to folic acid. The first is concerned with the assessment of folic acid deficiency. The second is concerned with the measurement of folic acid absorption. I shall then review these techniques in relation to the various groups of megaloblastic anæmia.

### ASSESSMENT OF FOLIC ACID DEFICIENCY

Folic acid deficiency is assumed to be present if a patient with a megaloblastic anæmia has a normal serum $B_{12}$ level or if treatment with vitamin $B_{12}$ fails to produce an adequate response. A subsequent response to folic acid is usually considered to indicate folic acid deficiency. This ignores the possibility that such a megaloblastic anæmia may be due, not to folic acid deficiency, but to interference with utilization of this vitamin, and the best-known example of this group is the megaloblastic anæmia due to the use of anticonvulsant drugs.

*The plasma clearance of folic acid.*—We have attempted to assess folic acid deficiency by the rate of clearance from the plasma of an intravenous dose of folic acid (Chanarin, Mollin and Anderson, 1958). The dose we used was 15 $\mu$g./kg. body weight. A person weighing 70 kilograms, therefore, received 1 mg. of folic acid. This was given intravenously and a blood sample collected three minutes, fifteen minutes and thirty minutes after the injection. The folic acid content of the serum of these samples was estimated by microbiological assay using a mutant of *Streptococcus fæcalis* as the test organism (Jukes, 1955; Chanarin, Anderson and Mollin, 1958).

*The clearance in normal subjects.*—The results of such a clearance test in 50 control subjects are shown in Fig. 1.

The serum folic acid concentration three minutes after the injection ranged from 75 $\mu$mg.–186 $\mu$mg./ml. (mean 127 $\pm$ 14 $\mu$mg.). It fell to 21 $\mu$mg.–80 $\mu$mg./ml. at fifteen minutes (mean 40 $\pm$ 2 $\mu$mg.) and to 4 $\mu$mg.–49 $\mu$mg./ml. at thirty minutes (mean 20 $\pm$ 9 $\mu$mg.).

[1] Joseph Senior White Research Fellow, Royal College of Physicians.
[2] In receipt of a grant from the Medical Research Council.

There are two phases in the normal clearance of injected folic acid, for, if at three minutes all the injected folic acid was still in the plasma the calculated serum level would be over 200 μmg./ml. The mean level was, in fact, 127 μmg./ml. 60% of the injected dose has, therefore, been cleared from the plasma in the first three minutes after the injection. The subsequent rate of clearance was slower. The first rapid phase represents immediate uptake of folic acid by tissues, little of this dose being excreted by the kidneys (Spray *et al.*, 1951; Chanarin, 1957). The tissues which are normally "unsaturated" for folic acid become "saturated" in this phase so that the rest of the folic acid is then removed more slowly.

If this degree of "unsaturation" of the tissues for folic acid is reduced—and this can be done by giving the subject some folic acid twenty-four hours before the clearance test—then the three-minute serum level is considerably higher, and the subsequent rate of clearance slower.

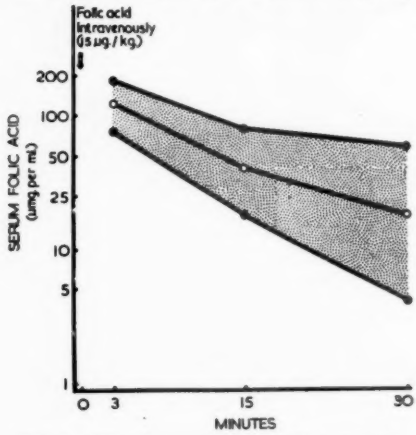



FIG. 1.—The plasma clearance of intravenous folic acid in 50 normal subjects.

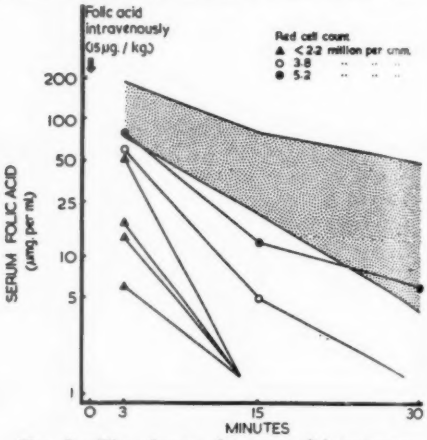



FIG. 2.—The plasma clearance of intravenous folic acid in 6 patients with untreated megaloblastic anæmia associated with idiopathic steatorrhœa and impaired absorption of folic acid. The stippled area represents the range of clearance in normal subjects.

*The clearance in folic acid deficiency.*—In patients with a megaloblastic anæmia in whom folic acid deficiency could be anticipated, i.e. patients with idiopathic steatorrhœa and impaired absorption of folic acid, a different pattern of folic acid clearance was found. This is shown in Fig. 2 which compares the clearance found in 50 normal subjects (stippled area) with the rate of clearance in 6 such patients.

The rate of clearance is more rapid than normal in all the patients irrespective of the degree of anæmia. In the most anæmic patients (those with red cell counts of less than 2·2 million per c.mm.) the serum folic acid concentration three minutes after the injection was lower than in normal subjects, and there was no measurable folic acid at fifteen minutes. In patients with very little anæmia and minimal megaloblastic change the rate of clearance may be less rapid. In these patients the three-minute serum folic acid level is usually either normal or slightly below the normal range; the fifteen-minute serum level is always reduced; and there is usually no folic acid in the thirty-minute sample.

These results indicate that this test can be used to detect folic acid deficiency. An increased rate of clearance of injected folic acid indicates an increase in the degree of "unsaturation" of the tissues for folic acid—in other words, folic acid deficiency.

## The Absorption of Folic Acid

The absorption of folic acid has been assessed by giving a small oral dose of the vitamin and measuring the changes in serum concentration over the next few hours (Chanarin, Anderson and Mollin, 1958). The type of pattern found is shown in Fig. 3. As the folic acid is absorbed there is a rise in the serum level of the vitamin with a peak concentration at about one to two hours.

The results of such an absorption test in 55 normal subjects are shown in Fig. 4. The oral dose of folic acid used was 3·0 mg. In all subjects the peak serum level was greater than 40 μmg./ml. serum and the mean peak concentration in the whole group was 96 ± 4 μmg. ml. serum. Failure to attain a serum level of 40 μmg./ml. we regard as evidence of impaired absorption of folic acid.

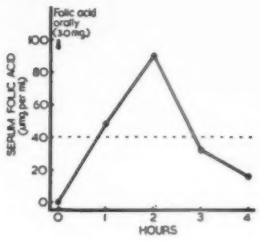



FIG. 3.—Serum folic acid concentration in a normal subject after an oral dose of 3·0 mg. of folic acid.

FIG. 3.

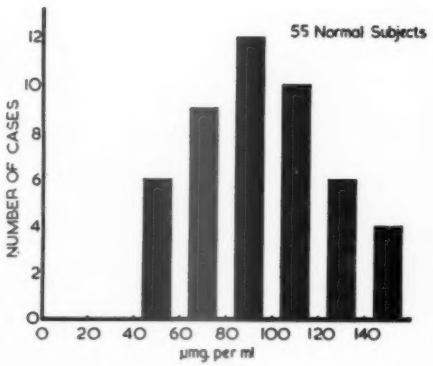



FIG. 4.—The peak serum folic acid concentration in 55 normal subjects after an oral dose of 3·0 mg. of folic acid.

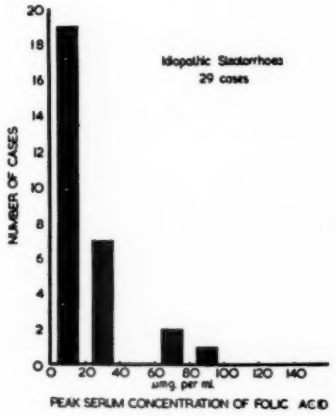



FIG. 5.—The peak serum folic acid concentration, in 29 patients with idiopathic steatorrhœa, after an oral dose of 3·0 mg. of folic acid.

## RESULTS IN THE MEGALOBLASTIC ANÆMIAS

*Megaloblastic Anæmia Associated with Idiopathic Steatorrhœa*

*The absorption of folic acid.*—The results of a folic acid absorption test in 29 patients with idiopathic steatorrhœa, 19 of whom had a megaloblastic anæmia, are shown in Fig. 5. In 26 patients the peak serum level after the oral dose was subnormal (<40 μmg./ml.) suggesting that there was impaired absorption of the vitamin.

The other 3 patients had peak folic acid concentrations within the normal range and were therefore presumably able to absorb folic acid in a normal manner. All 3 had a mild megaloblastic anæmia which was not due to vitamin $B_{12}$ deficiency.

These results either imply that the absorption test was insufficiently sensitive to detect impaired absorption of folic acid in these 3 patients, or that the megaloblastic anæmia in these patients was due to some cause other than deficiency of folic acid associated with malabsorption of the vitamin. The results of the folic acid clearance test in these 2 groups suggest that the latter alternative may be correct.

*The clearance of folic acid.*—The results of a folic acid clearance test in 6 patients who were unable to absorb folic acid normally are given in Fig. 2. The injected folic acid was cleared more rapidly than normal in all, irrespective of the degree of anæmia. These rapid clearances appear to confirm folic acid deficiency as the cause of the anæmia and this deficiency is presumably due to impaired absorption of the vitamin as suggested by Girdwood (1953).

On the other hand the folic acid clearance test was normal in 2 of the 3 patients who also absorbed folic acid normally. Nevertheless these 2 patients had a megaloblastic anæmia which required folic acid. It seems probable that this megaloblastic anæmia is not due to folic acid deficiency, but to an interference with its utilization, perhaps by antagonists. The abnormal intestinal bacterial flora often present in these patients may well provide a source for such folic acid antagonists.

*Megaloblastic Anæmia Associated with the Use of Anticonvulsant Drugs*

A group of megaloblastic anæmias which are undoubtedly caused by drugs used in the treatment of epilepsy (Badenoch, 1954; Hawkins and Meynell, 1954; Fuld and Moorhouse, 1956; Hobson *et al.*, 1956) might be considered at this point.

We have studied 2 patients with severe megaloblastic anæmia following the use of primidone (Chanarin, Elmes and Mollin, 1958), and one following barbiturate therapy. In all three the clearance of intravenous folic acid was normal. This would seem to exclude any significant degree of folic acid deficiency in these patients and suggests that the anæmia stems from interference by the drug with the utilization of available folic acid.

On the other hand, 2 patients who developed severe megaloblastic anæmia while receiving phenytoin sodium as well as 3 patients who received various combinations of these drugs cleared injected folic acid very rapidly. In these patients the anæmia was associated with folic acid deficiency. All, however, require treatment with folic acid.

*Megaloblastic Anæmia of Pregnancy*

Megaloblastic anæmia associated with pregnancy is probably the commonest form of megaloblastic anæmia requiring treatment with folic acid. The data provided by Goodall (1957) suggests that its incidence in this country may even be as high as 1% of all pregnancies.

The folic acid clearance was extremely rapid in all the patients we have studied, being as rapid as in severe megaloblastic anæmia associated with malabsorption of folic acid. The anæmia is therefore a folic acid deficiency state. At least three factors should be considered: (1) the absorption of folic acid, (2) the folic acid requirements of the fœtus, and (3) the dietary intake of folic acid.

(1) *The absorption of folic acid.*—Pregnant patients do not absorb folic acid as well as control subjects (Chanarin *et al.*, 1959). The mean peak serum folic acid concentration in 23 pregnant subjects after an oral dose of folic acid was 48 μmg./ml. as compared with 96 μmg./ml. in the normal control group (Fig. 6). However, the absorption of folic acid in 7 patients with treated megaloblastic anæmia of pregnancy was no different from that found in the pregnant controls, so that this factor alone does not produce the anæmia.

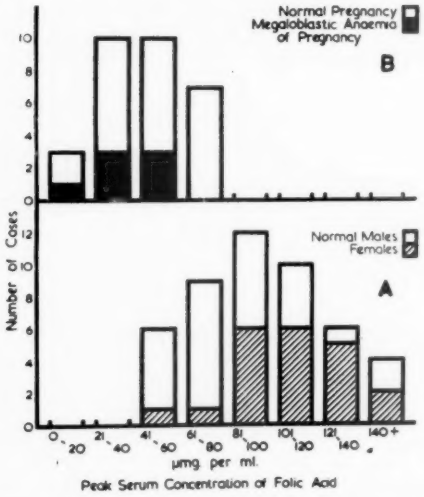



FIG. 6.—The peak serum folic acid concentration in 23 normal pregnant subjects and 7 patients with megaloblastic anæmia of pregnancy who had been treated with folic acid. The results in 55 control subjects are also given.

(2) *The folic acid requirements of the growing fœtus.*—Megaloblastic anæmia appears most frequently during the last two months of pregnancy. This is also the time of most rapid growth of the fœtus. Furthermore in twin pregnancy the incidence of megaloblastic anæmia is ten times as high as in single pregnancy.

Folic acid requirements in normal pregnancy were studied by following the clearance of injected folic acid in these patients (Chanarin, MacGibbon, Mollin and O'Sullivan, 1959). A moderately rapid clearance of injected folic acid is common in the last two months of pregnancy. The rate of clearance is most rapid in patients with twin pregnancy where it may be similar to the clearance in patients with megaloblastic anæmia due to folic acid deficiency. It seems reasonable to attribute these results to the increased requirements for folic acid by the growing fœtus.

(3) *The dietary intake of folic acid in pregnancy.*—Thompson (1957) found that megaloblastic anæmia of pregnancy in this country was more frequent in the winter months, and this, he suggested, was due to a diminished availability of green vegetables which are a source of folic acid.

However, a seasonal incidence of megaloblastic anæmia need not necessarily be associated with changes in diet. Rifkin (1958) found that of 396 cases of megaloblastic anæmia seen in a large hospital in Durban, South Africa, over a three-year period 140 (37%) occurred in

the hot months of the year, i.e. November, December and January, as compared with 75 cases (19%) in May, June and July. As with the patients described by Wills (1932) and Manson-Bahr (1951), a very large proportion of the patients were pregnant women. There was no evidence that the diet was particularly defective during the hot months. On the other hand, this was the time of the year when gastro-intestinal infection was prevalent.

The increased demand for folic acid by the growing fœtus, coupled with relatively poor absorption of this vitamin, tends to the production of folic acid deficiency in pregnancy. Possibly under these circumstances a good intake of folic acid may prevent the onset of megaloblastic change, and a poor diet may precipitate it.

*Megaloblastic Anæmia Due to an Increased Demand for Folic Acid*

Another group of megaloblastic anæmias, which has not received adequate recognition, also appears to be caused by an increased demand for folic acid. This is the group of megaloblastic anæmias associated with leukæmia and related disorders and with hæmolytic anæmia. The presence of megaloblastic change in leukæmia was recognized by Von Leube (1902), and in carcinomatosis by Ehrlich and Lazarus (1900). An example of this type of case is illustrated in Fig. 7.

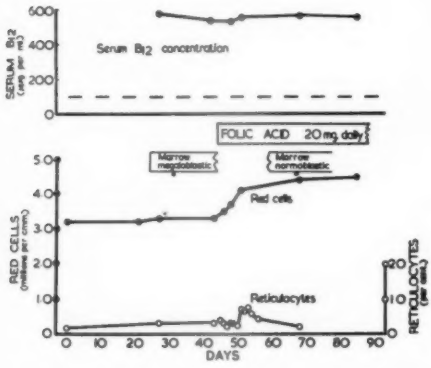



FIG. 7.—The hæmatological response to treatment of a patient with megaloblastic anæmia and chronic myelofibrosis.

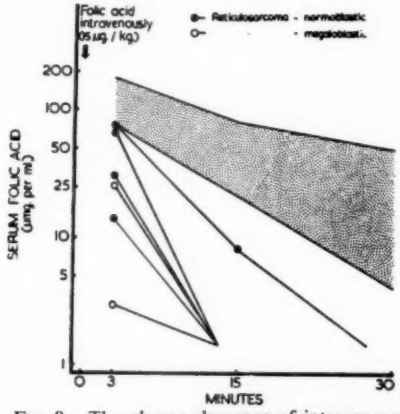



FIG. 8.—The plasma clearance of intravenous folic acid in 6 patients with reticulosarcoma. In 2 patients whose clearances are indicated by open circles, there was a severe degree of megaloblastic erythropoiesis.

The patient was a woman of 72 with chronic myelofibrosis. The red cell count was 3·2 million/c.mm., the blood film was macrocytic and marrow aspiration yielded rather scanty fragments which showed megaloblastic erythropoiesis. There was no vitamin $B_{12}$ deficiency because serum $B_{12}$ concentration was normal (590 $\mu\mu$g./ml.). Folic acid deficiency was confirmed by an extremely rapid clearance of injected folic acid from the plasma. In fact, the clearance was complete at the time of taking the first blood sample three minutes after the injection. The absorption of folic acid was normal. She responded to oral folic acid with a return of normoblastic erythropoiesis and a sustained rise in the red cell count.

This increased rate of clearance of injected folic acid is not confined to those patients with myelofibrosis who have a megaloblastic anæmia. 4 other patients with chronic myelofibrosis we have studied had a rapid clearance of injected folic acid.

Chronic myelofibrosis is one of a group of conditions in which there is a very large demand for folic acid. Other conditions in this category are leukæmia, hæmolytic anæmia, reticulosarcoma, myeloma and carcinomatosis.

The clearance of injected folic acid in 6 patients with reticulosarcoma is shown in Fig. 8. In all there is an abnormally fast clearance of injected folic acid suggesting folic acid deficiency. In 2 patients there was a severe degree of megaloblastic erythropoiesis. This increased demand for folic acid then forms the background for a megaloblastic anæmia which may arise.

The increased demand for folic acid may not be the only factor in causing the anæmia in these conditions. Malabsorption of fat, glucose, vitamin $B_{12}$ as well as folic acid, may occur in a surprising number of these patients.

These observations were all made in untreated patients, but, of course, treatment with folic acid antagonists and 6-mercaptopurine may produce megaloblastic change (Berman *et al.*, 1949).

*Vitamin $B_{12}$ Deficiency*

The classical vitamin $B_{12}$ deficiency state occurs in Addisonian pernicious anæmia.

The clearance of injected folic acid in 12 patients with untreated Addisonian pernicious anæmia is shown in Fig. 9. Rapid clearances were found in all the patients with an initial red cell count of less than 2·0 million/c.mm. and the clearances were most rapid in those whose red cell counts were less than 1·7 million/c.mm. The clearances were normal in patients with red cell counts of more than 3·0 million/c.mm. Thus in pernicious anæmia folic acid deficiency is present when the degree of anæmia has become moderately severe.

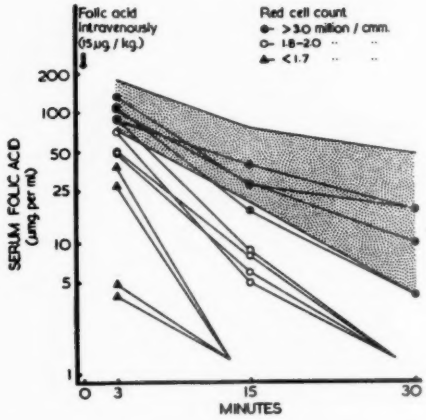



FIG. 9.—The plasma clearance of intravenous folic acid in 12 patients with untreated Addisonian pernicious anæmia.

Although in general there is a fair correlation between the severity of the anæmia in this condition and the serum $B_{12}$ level—very low serum $B_{12}$ levels being found in the most anæmic patients (Mollin and Ross, 1952)—there are many exceptions. In particular, patients with subacute combined degeneration of the cord may have little or no anæmia but invariably have very low serum $B_{12}$ levels (Mollin and Ross, 1954). It is not, therefore, the degree of vitamin $B_{12}$ depletion alone which determines the development of anæmia in patients with Addisonian pernicious anæmia.

On the other hand there is a very clear relationship between the degree of anæmia and the rate of clearance of injected folic acid, and this suggests that anæmia in these patients is due to the development of a secondary folic acid deficiency.

In spite of the presence of folic acid deficiency as indicated by the rapid clearance, patients with primary $B_{12}$ deficiency do not respond to the dose of folic acid used in the clearance test. This is in contrast to the result often found in uncomplicated folic acid deficiency where there may be a significant reticulocyte response with a return towards normoblastic erythropoiesis in the marrow.

## SUMMARY

Table II summarizes our views on the pathogenesis of these megaloblastic anæmias.

TABLE II.—FOLIC ACID AND THE MEGALOBLASTIC ANÆMIAS

| *Folic Acid Deficiency* | *Impaired Utilization of Folic Acid* |
|---|---|
| Malabsorption: | Drugs: |
| Idiopathic steatorrhœa | Antagonists |
| Tropical sprue | Anticonvulsants |
| Other malabsorption syndromes | Vitamin $B_{12}$ deficiency |
| Increased demand: | *Uncertain Factors* |
| Fœtus in pregnancy | Abnormal intestinal flora |
| Leukæmia | |
| Reticulosarcoma | |
| Myelofibrosis | |
| Hæmolytic anæmia | |
| (Dietary deficiency) | |

There are 2 major groups. The first is folic acid deficiency; the second is impaired utilization of the vitamin. Folic acid deficiency may arise from impaired absorption; but it may also arise from the presence of conditions which produce an increased demand for folic acid. Reduced dietary intake may be a factor.

impaired utilization may be due to folic acid antagonists such as aminopterin and amethopterin, and also to the anticonvulsant drugs used in the treatment of epilepsy. Impaired utilization may also result from a primary vitamin $B_{12}$ deficiency.

The role of bacteria in producing megaloblastic anæmia is uncertain. They may interfere with the absorption of folic acid, as in tropical sprue, and with the absorption of vitamin $B_{12}$, as in patients with anatomical lesions of the small intestine. Whether these bacteria can also function by producing substances which act as folic acid antagonists has not been demonstrated.

## REFERENCES


BADENOCH, J. (1954) *Proc. R. Soc. Med.*, **47**, 426.
BERMAN, L., AXELROD, A. R., VON DER HEIDE, E. C., and SHARP, E. A. (1949) *Amer. J. clin. Path.*, **19**, 127.
CHANARIN, I. (1957) Unpublished observations.
——, ANDERSON, B. B., and MOLLIN, D. L. (1958) *Brit. J. Hæmat.*, **4**, 156.
——, ELMES, P. C., and MOLLIN, D. L. (1958) *Brit. med. J.*, ii, 80.
——, MACGIBBON, B. H., MOLLIN, D. L., and O'SULLIVAN, W. J. (1959). To be published.
——, MOLLIN, D. L., and ANDERSON, B. B. (1958) *Brit. J. Hæmat.*, **4**, October.
EHRLICH, P., and LAZARUS, A. (1900) Histology of the Blood. Cambridge.
FULD, H., and MOORHOUSE, E. H. (1956) *Brit. med. J.*, i, 1021.
GIRDWOOD, R. H. (1953) *Lancet*, ii, 53.
GOODALL, H. B. (1957) *J. clin. Path.*, **10**, 248.
HAWKINS, C. F., and MEYNELL, M. J. (1954) *Lancet*, ii, 737.
HEINLE, R. W., WELCH, A. D., SCHARF, V., MEACHAM, G. C., and PRUSSOFF, W. H. (1952) *Trans. Ass. Amer. Phycns.*, **65**, 214.
HOBSON, Q. J. G., SELWYN, J. G., and MOLLIN, D. L. (1956) *Lancet*, ii, 1079.
JUKES, T. H. (1955) In: D. Glick's Methods of Biochemical Analysis. New York; **2**, 121.
MANSON-BAHR, P. E. C. (1951) *J. trop. Med.* (*Hyg.*), **54**, 90.
MOLLIN, D. L., and ROSS, G. I. M. (1952) *J. clin. Path.*, **5**, 129.
——, —— (1954) *Proc. R. Soc. Med.*, **47**, 428.
RIFKIN, S. J. (1958). Unpublished observations.
ROSENTHAL, H. L., and SARETT, H. P. (1952) *J. biol. Chem.*, **199**, 433.
ROSS, G. I. M. (1950) *Nature, Lond.*, **166**, 270.
SPRAY, G. H., FOURMAN, P., and WITTS, L. J. (1951) *Brit. med. J.*, ii, 202.
THOMPSON, R. B. (1957) *Lancet*, i, 1171.
VON LEUBE, W. (1902) *Dtsch. Klin.*, **3**, 177.
WILLS, L. (1932) *Proc. R. Soc. Med.*, **25**, 1720.


# Hypoplastic Anæmia in Infancy

By JOHN L. STAFFORD, M.B.

*London*

SIGNIFICANT anæmia, resulting from marrow hypoplasia, is uncommon in infancy yet it is seen sufficiently frequently for its diagnosis to present a problem. Many papers on this topic have been written during the twenty years since Josephs (1936) and Diamond and Blackfan (1938) initially described their cases of familial hypoplasia, and classification has become diffuse with the recording of previously undescribed features, many being but variations on the same theme. This complexity is probably unnecessary and an attempt will be made to simplify the various categories into three main groups.

Table I shows the gradation of effect between the various types of marrow hypoplasia.

TABLE I.—THE GRADATION OF EFFECT IN MARROW FAILURE IN CHILDHOOD

1. Total (pancytopenic) marrow failure
2. Failure of erythropoiesis possibly associated with agranulocytosis or pancytopenia
3. Isolated failure of erythropoiesis (pure red cell aplasia)

Marrow response may be limited. In the majority of instances the organ has failed as a whole and all cellular products are diminished. Some patients, however, suffer preponder-

antly from red cell aplasia with a greater or lesser degree of agranulocytosis or thrombocytopenia; while in some, the marrow failure is apparently restricted to erythropoietic function.

Table II summarizes the various syndromes with parenthetical reference to the better-known papers on each topic.

TABLE II.—THE HYPOPLASTIC ANÆMIAS OF INFANCY AND CHILDHOOD

| | | | |
|---|---|---|---|
| Total (Pancytopenic) marrow failure | (1) Secondary | Toxic; infective; allergic<br>Marrow replacement (metabolic; neoplastic)<br>Post-irradiation | |
| | | Hypersplenism (Doan and Wright, 1946)<br>Peripheral pancytopenia | |
| | (2) ? Genetically determined | "Stationary" (Palmen and Vahlquist, 1949)<br>Familial (Dacie and Gilpin, 1944; Estren and Dameshek, 1947)<br>Multiple congenital defects (Fanconi, 1927)<br>"Non-hæmolytic" anæmia of newborn (Smith, 1953) | |
| | (3) Secondary | Deficiency syndromes<br>Folic acid—goat's milk anæmia; ascorbic acid<br>Marrow "exhaustion"<br>Hæmolytic disease of newborn<br>Bone-marrow arrest (Dameshek and Bloom, 1948)<br>Occult placental hæmorrhage (Wiener, 1948)<br>Crises in hereditary hæmolytic syndromes (Owren, 1948) | |
| Erythropoietic failure with pancytopenia of varying severity | (4) ? Genetically determined | Maturation defect<br>Pure aplastic anæmia (Kaznelson, 1922)<br>Erythrophthisis (Baar, 1928) | Marrow arrest at erythroblast stage |
| | | Normoblastic arrest (Lelong *et al.*, 1951)<br>Erythrogenesis imperfecta (Cathie, 1950) | Early (normoblast) or late (reticulocyte) arrest |
| | | Congenital hypoplasia (Diamond and Blackfan, 1938)<br>Aregenerative anæmia (Vogel *et al.*, 1937) | No apparent maturation arrest |
| | | Tryptophane metabolism defect<br>Anthranilic aciduria (Altman and Miller, 1953) | |
| Isolated failure of erythropoiesis (other marrow functions unaffected) | (5) Immunological | Acute allergic erythroblastopenia (Gasser, 1949)<br>Renal failure (Gasser, 1955)<br>Anuria (Richet *et al.*, 1954)<br>Thymic tumour (Chalmers, 1954) | |
| | | Iso-immune antibodies (Smith, 1949)<br>Auto-immune antibodies (Bonham-Carter *et al.*, 1955) | |

(1) Total marrow failure is usually secondary to some easily recognized insult to function, either toxic, infective or allergic; it may follow marrow replacement as in the so-called metabolic disorders, in marble bone disease or from neoplastic infiltration; or it may result from irradiation. Hypersplenism is quoted in this context for it may present with peripheral evidence of pancytopenic marrow failure yet, of course, with excess activity in the marrow itself: it must be rare in infancy, but Doan and Wright (1946) believed one of their original cases of hypersplenism to be congenital.

(2) In some children pancytopenic marrow hypofunction has no apparent cause; a familial incidence and the coincidence of multiple structural defects suggest that these are constitutional or genetically determined. The Fanconi (1927) type is perhaps the most severe of this form. Smith (1953) refers to a transitory anæmia in which the marrow of the otherwise normal child fails to respond to the usual post-natal stimuli and erythropoiesis is delayed for a few weeks; for this, he has adopted the term "non-hæmolytic" anæmia of the newborn.

(3) In some instances of secondary marrow failure, red cell hypoplasia is predominant, but leucopenia and thrombocytopenia often supervene. This is possibly the result of exhaustion

from chronic over-stimulation—in a minor form it frequently follows hæmolytic disease of the newborn.

In some children failure appears to be confined to red cell formation yet marrow function otherwise remains normal. Again, exhaustion may cause this change. In the hereditary hæmolytic syndromes it is probably the result of chronic over-stimulation and is referred to by Owren (1948) as a potential cause of the hæmolytic crises; in a similar fashion, occult placental hæmorrhages may result in the same change (Wiener, 1948).

(4) This isolated failure of erythropoiesis may have no apparent cause. Kaznelson (1922) first recorded an example of pure aplastic anæmia in an elderly man and Baar (1928) described what he termed erythrophthisis in a 3-year-old child. In the marrow of such cases red cell precursors of all types are missing.

Alternatively erythroblasts may be present, but their later development is interfered with. In the cases of erythrogenesis imperfecta, described by Cathie (1950), the block appeared to be at the reticulocyte stage. Lelong *et al.* (1951) have reported similar findings but with the maturation arrest at the normoblast stage.

This group also includes the well-known variants described by Josephs (1936) and Diamond and Blackfan (1938) as familial hypoplastic anæmia, in which there may be no demonstrable marrow abnormality. Recently, in some of these latter cases, an underlying defect of tryptophane metabolism has been demonstrated, with the presence of anthranilic acid in the urine (Altman and Miller, 1953). It seems that this group as a whole may well be constitutional, may be complicated by genetically determined abnormalities, and may be associated with a defect of metabolism.

(5) Finally, there is a group of rare syndromes in which the red cell aplasia is usually acute and may be transient and the underlying pathology appears to be due to immune mechanisms. Gasser (1949) has described acute allergic erythroblastopenia, usually following within ten days of an infectious or toxic episode. Similar changes have been found in both acute and chronic nephritis (Gasser, 1955) and in acute anuria (Richet *et al.*, 1954). Chalmers (1954) has referred to red cell aplasia co-existent with thymic tumours in adults; recently he has mentioned to me a child with red cell aplasia in whom reticulocytes were demonstrated for a short period, following the removal of a normal thymus.

Some half a dozen cases have been described of acute red cell aplasia associated with an iso-immune reaction. Smith's (1949) original case was due to anti-A iso-antibodies, others have been associated with anti-D antibodies and a case described by Bonham-Carter, Cathie and Gasser (1954) was apparently due to non-specific incomplete cold auto-antibodies. The case I am about to describe appears to come into this latter category.

It seems that the majority of cases of marrow failure in childhood are secondary to external or foreign stimuli; some are the result of a genetically determined dyscrasia; a few are due to iso- or auto-immune mechanisms (Table III).

TABLE III.—HYPOPLASTIC ANÆMIA IN INFANCY

| | |
|---|---|
| (1) | Secondary to external or foreign stimuli (Including "exhaustion" from chronic over-stimulation) |
| (2) | Genetically determined dyscrasia (Including metabolic defects) |
| (3) | Iso- or auto-immune mechanisms |

## CASE REPORT

Linda M. is now 12 months old and very well, but she has passed through a transient phase of profound erythropoietic hypoplasia, analogous to the pure red cell aplasia described by Lescher and Hubble (1932). Her story is of particular interest for it shows an apparent etiological link between neonatal marrow failure and iso-immunization.

I am most grateful to Dr. Ursula James for permission to discuss a case under her care at the Victoria Hospital for Children, Chelsea.

Linda arrived as the fourth pregnancy of a rhesus-negative Irish spinster, all sired by the same apparently homozygous positive Negro father. The first pregnancy had miscarried; the next two babies received successful exchange transfusions and are growing up as healthy but total charges of the London County Council. Linda was born on the pavement outside hospital with the aid of a passing policeman, but the delivery, at term, was otherwise normal. There was a maternal serum titre of 1 : 4,096 blocking anti-D antibodies and the child was jaundiced. An immediate exchange transfusion of 400 ml. whole blood was given without complication and she was discharged on the 16th day, having regained her birth weight of 6¼ lb.

Within a few days, however, the hæmoglobin dropped rapidly to 5·2 grams/100 ml. and, on the 24th day, she was admitted for the first time to the Victoria Hospital for Children. Marrow aspiration revealed an almost complete absence of red cell precursors, but a normal complement of megakaryocytes and the white cell series. Scattered throughout were small cells containing dense, darkly staining nuclei and an almost invisible cytoplasm—so-called

hæmatogones. In the peripheral stream the white cells and platelets were normal: reticulocytes could not be found and differential agglutination tests failed to reveal any of the child's own D-positive red cells.

(These were subsequently typed as Group O rhesus positive (CcDdee); the mother was group O rhesus negative (cde/cde); and the putative father group O rhesus positive (CcDee).)

Auto-agglutination at room temperature had created difficulty during cross-matching for the exchange transfusion, and this was still present at the 24th day when the red cells of *both* mother and child gave a positive direct Coombs' reaction. In addition to the high titre of anti-D antibodies, a cold incomplete auto-antibody of non-gamma-globulin type was present to a titre of 1:256.

On the 28th day 200 ml. whole blood were transfused without incident; Fig. 1 shows subsequent progress assessed by heel-stab hæmoglobin estimations. The hæmoglobin level again fell and a further 275 ml. whole blood were transfused on the 78th day. In comparison with the arbitrary 100/120 day expected survival of red cells after transfusion (Fig. 2) the first drop in hæmoglobin is most marked and probably partly due to the non-specific auto-immune antibodies incompletely removed by exchange transfusion: the second drop is less marked and there are two peaks which suggest minimal erythropoiesis, although reticulocytes were never demonstrated until the 101st day.

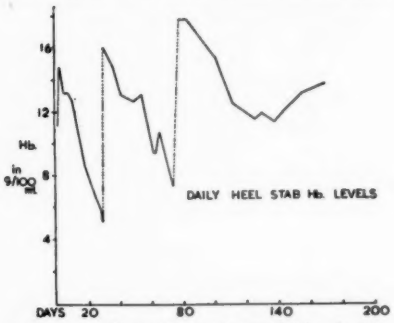



FIG. 1.—Percentage hæmoglobin levels during first 170 days. (Heel-stab determinations).

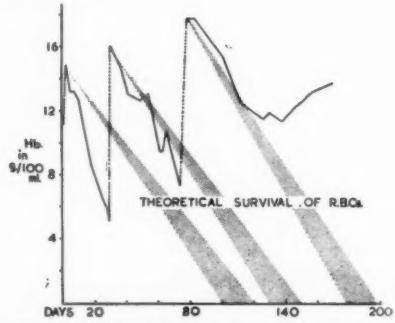



FIG. 2.—The decline in percentage hæmoglobin compared with theoretical survival of transfused red cells.

In the rapidly growing infant (Linda gained 11 lb. during the first 6 months) reference to the percentage hæmoglobin level is not an accurate index of progress. Body weight can be equated with total hæmoglobin mass by accepting an arbitrary blood volume of 40 ml. per lb. and in Fig. 3 Linda's weight curve has been applied to that of an average total hæmoglobin mass in a baby with similar weight-gain, based on average hæmoglobin levels during the first 175 days of life (MacKay, 1933; Horan, 1950).

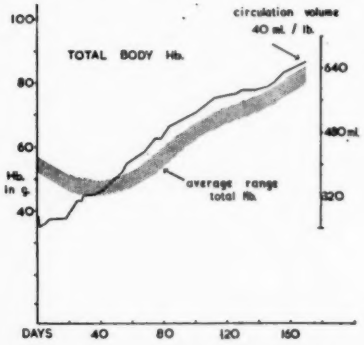



FIG. 3.—Increase of circulatory volume (40 ml./lb.) and total body hæmoglobin compared with average range for infants of similar age and weight-gain.

By plotting total body hæmoglobin instead of hæmoglobin percentage (Fig. 4) the apparent deficit during the first 100 days is minimized. On applying this curve to the arbitrary normal range for a child of this weight (Fig. 5) it is seen that the final transfusion of 275 ml. raised

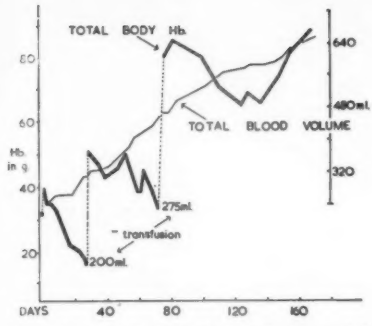



FIG. 4.—Total circulating body hæmoglobin plotted to compare with increase in weight and blood volume.

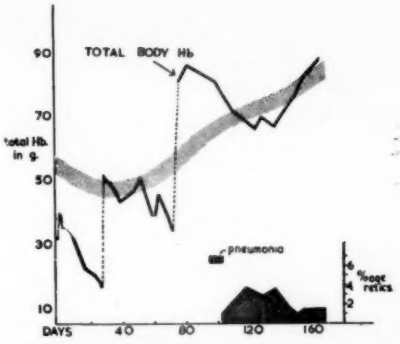



FIG. 5.—Total body hæmoglobin compared with average curve for infants of similar age and weight-gain.

the hæmoglobin mass beyond the required level; a transfusion of half this amount would have sufficed. It has been suggested that in the newborn a hæmoglobin level of less than 11·5 grams/100 ml. is necessary before optimum marrow stimulation is achieved. Therapy, therefore, may have had the paradoxical effect of delaying ultimate erythropoiesis beyond 100 days by maintaining a hæmoglobin level high enough to deprive the marrow of its usual anoxic stimulation.

Between 95 and 100 days, however, an intercurrent pneumonia occurred and it is possible that the consequent slight degree of anoxia may have contributed to the appearance of reticulocytes for the first time immediately afterwards. Since then there has been no evidence of marrow failure; progress has been entirely normal, although the reticulocyte response never rose above 4%. No other abnormalities could be demonstrated, there was no splenomegaly and nothing to suggest a structural or metabolic defect. Liver function tests, including plasma bilirubin, were normal, and Schumm's test for methæmalbumin consistently negative. The serum iron level was a low normal (110 γ/100 ml.). Differential agglutination by the Ashby technique revealed a few D-positive cells by the 75th day and these slowly increased in number until, by the 100th day, they represented about 30% of the circulating total. Serial estimations for fœtal hæmoglobin were negative; serum and hæmoglobin electrophoretic patterns were normal; anthranilic aciduria was not present, Ham's test with acidified serum was negative, and no cold hæmolysin could be demonstrated. Repeated white cell and platelet estimations showed these to be normal or, during the phase of pneumonia, slightly elevated.

A repeated marrow aspiration on the 78th day showed early evidence of recovery of erythropoietic function with the so-called hæmatogones still predominating; early and intermediate normoblasts were now present in substantial numbers. Since that time progress has been entirely normal and, at the age of 1 year, the baby has developed without any evidence of pathological change.

## DISCUSSION

This case shows isolated failure of erythropoiesis during the first 75 to 100 days of life, which was associated with apparently normal function in all other respects. Coincidentally there was hæmolytic disease of the newborn from anti-D iso-antibodies and, as an additional finding, an incomplete non-specific auto-antibody was present in both the mother and child. The differential diagnosis would appear to lie between the marrow exhaustion usually found in hæmolytic disease of the newborn; the so-called "non-responsive" non-hæmolytic anæmia of the newborn referred to by Smith (1953) and marrow failure due to immune mechanisms of the type referred to by Gasser (1957). As regards hæmolytic disease of the newborn, the relative hypoplasia of erythropoiesis which follows is generally associated with leucopenia and sometimes thrombocytopenia: it is almost invariably transient and recovery takes place within 6 weeks. The non-responsive anæmia of the newborn is often more transient and, although the anomaly may be limited to red cell formation, recovery is complete within 2 to 3 weeks of birth. In this case recovery did not take place until 14 weeks, although this may have been delayed somewhat by transfusion therapy.

The presence of hæmatogones in the marrow during this period is a finding which is difficult to explain; these cells are described as being similar in morphology to the small lymphocyte but are widely regarded as red cell precursors which have, in some way, become abnormal. Morphologically they do not appear to be immature and, whilst accepting that they may be red cell precursors, it is difficult to believe that they are not differentiated. They may represent an abnormal form of differentiation indicating damage to the reticulo-

endothelial system by which they are produced. Their presence in the marrow appears to be evidence of fundamental change which is not to be expected from simple marrow exhaustion but may be due to circulating iso- and auto-antibodies.

If iso-antibody formation were to be associated with marrow damage, the occurrence of isolated erythropoietic failure would be expected more frequently than in fact is the case. It is suggested, therefore, that the coincidental presence of an excess of circulating non-specific cold auto-antibodies has provided an additional feature leading to marrow disorder. It is unfortunate that the non-gamma-globulin type of antibodies demonstrated on the 24th day were not examined in greater detail; by the time their importance was appreciated they were no longer demonstrable in either the mother or child.

There remains the problem of where the damage might occur. Antigenicity is easily demonstrated in the adult erythrocyte but it is not known at what stage of maturation such antigenic properties become manifest. It would appear possible, and Gasser (1957) has referred to this, that antibodies might be formed against antigens on the surface of erythroblasts and their immediate precursors; this would, in part, explain the complete failure of an isolated feature of marrow function without implication of the other proliferating cell series. In this context, the hæmatogone may represent an aberrant erythroid maturation caused by immunological damage to the reticulo-endothelial erythropoietic mechanisms.

REFERENCES


ALTMAN, K. I., and MILLER, G. (1953) *Nature, Lond.*, **172,** 868.
BAAR, H. S. (1928) *Folia hæmat., Lpz.*, **35,** 111.
BONHAM-CARTER, R. E., CATHIE, I. A. B., and GASSER, C. (1954) *Schweiz. med. Wschr.*, **84,** 1114.
CATHIE, I. A. B. (1950) *Arch. Dis. Childh.*, **25,** 313.
CHALMERS, J. N. M. (1954) *Brit. med. J.*, ii, 1514.
DACIE, J. V., and GILPIN, A. (1944) *Arch. Dis. Childh.*, **19,** 155.
DAMESHEK, W., and BLOOM, M. L. (1948) *Blood*, **3,** 1381.
DIAMOND, L. K., and BLACKFAN, K. D. (1938) *Amer. J. Dis. Child.*, **56,** 464.
DOAN, C. A., and WRIGHT, C. S. (1946) *Blood*, **1,** 10.
ESTREN, S., and DAMESHEK, W. (1947) *Amer. J. Dis. Child.*, **73,** 671.
FANCONI, G. (1927) *Jb. Kinderheilk.*, **117,** 257.
GASSER, C. (1949) *Helv. pædiat. acta*, **4,** 107.
—— (1955) *Sang*, **26,** 6.
—— (1957) *Pediat. clin. N. Amer.*, **4,** 445.
HORAN, M. (1950) *Arch. Dis. Childh.*, **25,** 110.
JOSEPHS, H. W. (1936) *Medicine, Baltimore*, **15,** 307.
KAZNELSON, P. (1922) *Verh. dtsch. Ges. inn. Med.*, **34,** 557.
LELONG, M., JOSEPH, R., POLONOWSKI, C., DESMONTS, G., and COLIN, J. (1951) *Arch. franç. Pédiat.*, **8,** 473.
LESCHER, F. G., and HUBBLE, D. (1932) *Quart. J. Med.*, **1,** 425.
MACKAY, H. M. M. (1933) *Arch. Dis. Childh.*, **8,** 221.
OWREN, P. A. (1948) *Blood*, **3,** 231.
PALMEN, K., and VAHLQUIST, B. (1949) *Acta hæmat.*, **4,** 273.
RICHET, G., ALAGILLE, D., and FOURNIER, E. (1954) *Pr. méd.*, **62,** 50.
SMITH, C. H. (1949) *Blood*, **4,** 697.
—— (1953) *J. Pediat.*, **43,** 457.
VOGEL, P., ERF, L. A., and ROSENTHAL, N. (1937) *Amer. J. clin. Path.*, **7,** 436.
WIENER, A. S. (1948) *Amer. J. Obstet. Gynec.*, **56,** 717.


## Primary Hæmorrhagic Thrombocythæmia

By SIDNEY SHAW, M.D., and R. A. M. OLIVER, M.A., D.M.
*London*

THROMBOCYTHÆMIA is relatively rare: it may be associated with other myeloproliferative disorders such as polycythæmia vera and myeloid leukæmia, and a secondary increase in platelets has been recorded following trauma, acute blood loss, splenectomy, and splenic atrophy.

Primary thrombocythæmia has been described by Epstein and Kretz (1930), Rowlands and Vaizey (1938), Reid (1940), Owren (1943), Fanger and co-workers (1954) and Pudlák and others (1955). An attempt has been made to differentiate between hæmorrhagic and non-hæmorrhagic forms of this condition by Hardisty and Wolff (1955). They found in the literature 18 previously recorded cases of primary thrombocythæmia with hæmorrhagic manifestations, and added 5 further cases.

We present here 3 cases of primary thrombocythæmia in each of whom hæmorrhage was observed; in 1 case thromboses were also recorded. Hardisty and Wolff (1955) demonstrated by the thromboplastin-generation test poor thromboplastin formation in their 5 patients; we have found a similar abnormality in the platelets of our cases. By comparison the platelets of 3 further patients with thrombocythæmia behaved normally in the thromboplastin-generation test; these were considered to be cases of secondary thrombocythæmia.

### Brief Case Notes

In these 3 patients with primary thrombocythæmia there was no relevant family history.

*Case I.*—Mrs. D. W., aged 55, had had Parkinson's disease diagnosed six years previously. When seen in January 1956 she gave a four-year history of repeated severe epistaxes.

Over the last two years the platelet count has varied between 1,150,000 and 3,830,000/c.mm.: the bleeding time, by Duke's method, was prolonged on one occasion to eight minutes. There has also been a mild hypochromic anæmia and the white cell count has never risen above 13,000/c.mm., an occasional myelocyte being seen. Epistaxes have recurred recently.

*Case II.*—Mr. R. G., aged 32, had been invalided from the Navy with a right hemiplegia with only partial recovery, considered due to cerebral thrombosis. In 1950 he had a bilateral sympathectomy for poor circulation in the feet. From early 1955 he had had occasional epileptic fits. When first seen in the summer of 1955 he had hæmaturia and ecchymoses in both thighs and in the left iliac region, during treatment with small doses of Dindevan given with careful laboratory control; the prothrombin time never rose to more than twice the control time.

The ECG showed evidence of previous anterior coronary infarction. His platelet count over the past two and a half years has varied between 700,000 and 1,800,000/c.mm. The hæmoglobin, red cell count, and volume of packed cells are normal and the leucocyte count has never risen above 14,000/c.mm.

*Case III.*—Mrs. E. A., aged 43, gave no relevant past history. She was admitted in November 1955. Two weeks before, she bled for seventy-two hours following a dental extraction, which had necessitated repeated blood transfusions. Over the past two years the platelet count has varied between 1,360,000 and 1,560,000/c.mm. The bleeding time was markedly prolonged on two occasions. The leucocyte count has remained normal. There have been no reports of further hæmorrhages.

In the above 3 patients there was no enlargement of lymph nodes or liver and the spleen was palpable in Case III only.

The brief case notes of the 3 patients considered as cases of secondary thrombocythæmia (post-hæmorrhagic type) are as follows; in none was there any relevant family history.

*Case IV.*—Mr. A. L., aged 55, was admitted in April 1957 with melæna following a hæmatemesis. There was no relevant past history. Investigation showed a hæmoglobin level of 3·9 g./100 ml., a white count of 11,000/c.mm. and platelets between 810,000 and 880,000/c.mm. Barium meal and gastroscopy were negative. His treatment included blood transfusion and iron. He has had no further hæmorrhage and a recent blood count shows a normal platelet level.

*Case V.*—Mrs. S. T., aged 84, was admitted in April 1957, in cardiac failure secondary to cardiac ischæmia. She had extensive ecchymoses from the left thigh to the ankle and petechiæ on the palate. Three years before she had had similar extensive ecchymoses of the left arm and chest. The platelet count was between 1,400,000 and 1,500,000/c.mm. on three occasions, the white cell count was 9,300/c.mm. An ascorbic acid excretion test confirmed a diagnosis of scurvy. She was discharged home after treatment with vitamin C and digitalis.

*Case VI.*—Miss C. S., aged 64. Four years previously had had a gastrectomy for a duodenal ulcer after repeated bouts of melæna. She attended in March 1957: one month before she had bled severely for twenty-four hours after dental extraction. Investigation showed a slight hypochromic anæmia, a leucocyte count of 12,000/c.mm. and platelet count between 930,000 and 1,130,000/c.mm. on three occasions.

There was no enlargement of liver, spleen or lymph nodes in any of these secondary cases.

### Investigation of Hæmostatic Function

Routine investigations of hæmostatic function in both primary and secondary cases did not detect any abnormality, except for the bleeding time (Duke's method), in Cases I and III, where abnormal prolongation was found on one occasion only in Case I (eight minutes), and two occasions in Case III (thirty-eight minutes and twenty minutes). The Hess test, coagulation time (Lee and White), prothrombin time and clot retraction were all normal. Platelet aggregation appeared to be increased in stained films, but was not excessive in wet preparations; platelet morphology appeared normal.

In view of the paradoxical association, especially in the first 3 patients, between the marked thrombocythæmia and the episodes of hæmorrhage, it was considered of interest to investigate the behaviour of their platelets in other aspects of hæmostatic function. Investigation of thromboplastin generation by the technique described by Biggs and Douglas (1953) was carried out: comparisons were made using three normal reagents (alumina plasma, for factor V and A.H.G., serum for factor VII and Christmas factor and platelet-poor plasma substrate), the variable factor being the platelet suspensions prepared from our patients and 3 normal controls. Platelet suspensions were prepared using the technique of Macfarlane and Biggs (1955), being first standardized at 100,000/c.mm. by direct counting under phase contrast with suitable saline dilution; the tests were repeated using platelet suspensions approximating to the number in the blood (the controls were standardized at approximately 250,000 platelets/c.mm.). The 3 cases designated as secondary thrombocythæmia were similarly investigated but only at platelet concentrations of 100,000/c.mm.

Thomboplastin generation was followed for six minutes. From a thromboplastin dilution curve (Fig. 1) the percentages of thromboplastin were derived.

## Results

From Fig. 2, where comparable numbers of platelets were used in patients and controls, it can be seen that thromboplastin generation was impaired for the first two minutes in all 3 cases of primary thrombocythæmia. Complete generation was only found in 1 patient, and here it was delayed, rising to normal at the fifth minute.

When the platelet concentrations of the patients investigated were used at the abnormally high levels found in their blood, a delay in thromboplastin formation was again seen as shown in Fig. 3. In only 1 patient was a normal level of thromboplastin obtained within the test period. In Case III the thromboplastin generation at the higher concentration of platelets was very poor and markedly less than at 100,000/c.mm. (a possible reason for this discrepancy will be discussed later).

In Cases IV, V and VI, which were considered as secondary thrombocythæmia, thromboplastin generation was normal as seen in Fig. 4, a 100% level being reached by the third minute in 2 cases and by the fourth minute in 1.

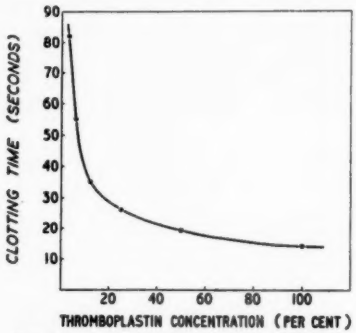



FIG. 1.—Thromboplastin dilution curve.

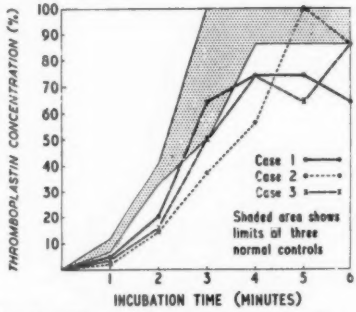



FIG. 2.—Thromboplastin generation. Platelet concentrations at 100,000/c.mm.

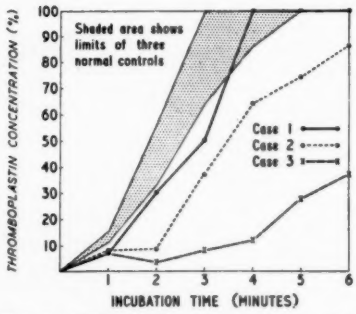



FIG. 3.—Thromboplastin generation. Platelet concentrations as in the blood.

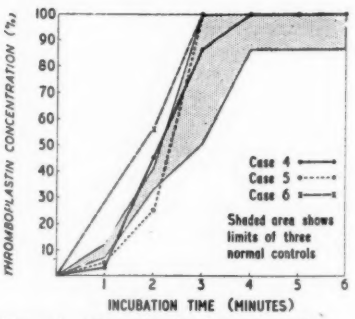



FIG. 4.—Thromboplastin generation. Platelet concentrations at 100,000/c.mm.

## Discussion

While some authors (Jasinki, 1949) have doubted that primary thrombocythæmia is an entity, in our 3 patients there was no evidence to suggest that the thrombocythæmia was secondary to any other condition such as leukæmia or other myeloproliferative disorder. The clinical and pathological features of primary thrombocythæmia have been recently reviewed by Hardisty and Wolff (1955). They describe the clinical course as being associated with repeated hæmorrhages from various sites with, in some cases, an additional tendency towards spontaneous venous thrombosis. In our 3 patients there were abnormal hæmorrhages: Case I suffered repeated epistaxes, in Case II there was hæmaturia and unaccountable hæmorrhage occurred into the tissues and in Case III there was severe hæmorrhage following dental extraction.

Hardisty and Wolff described arterial thrombosis in 1 patient of their series. In our Case II

the sudden onset of right hemiplegia and also cardiographic evidence of coronary infarction in a young man is strongly suggestive of arterial thrombosis; in addition this patient had required bilateral sympathectomy to relieve ischæmia of the feet. This is not an isolated association in thrombocythæmia; in a search through the literature we have found no less than 7 further cases with an associated ischæmia of the feet.

The case of Epstein and Kretz (1930) showed gangrene of the toes. A case described by Rowlands and Vaizey (1938) showed superficial gangrene of two toes with separation of small sloughs. Fanger *et al.* (1954) described a man with absent peripheral pulses in the lower limbs and incipient gangrene of the right great toe. Pridláh *et al.* (1955) described 4 cases of primary thrombocythæmia and in 3 of these there were circulatory insufficiencies demonstrable in the legs. Hardisty and Wolff (1955) noted 1 patient in their series who showed ischæmic ulceration of the right fifth toe.

The association was so strong that we feel that there is sufficient evidence to describe this as a definite syndrome. The mechanism of the ischæmia of the lower limbs is obscure but is presumably associated with dependency, stagnation and an increased liability to thrombosis associated with the high platelet count.

The occurrence of hæmorrhage in primary thrombocythæmia would appear to be paradoxical as platelets are enormously increased. However, by the thromboplastin-generation test we have shown that the platelet factor for thromboplastin formation was impaired in all 3 cases; this impairment was still present when the tests were repeated, using platelets in numbers comparable to the abnormally high levels in these patients.

All other tests of hæmostatic function, apart from the bleeding time, are normal in these cases, and it seems reasonable to assume that an abnormality in the platelets is responsible for the hæmorrhagic tendency.

These findings in primary thrombocythæmia agree with those of Hardisty and Wolff, who also demonstrated that in 12 cases of non-hæmorrhagic thrombocythæmia secondary to other causes such as myeloid leukæmia, polycythæmia vera, and myelofibrosis, there was no impairment of thromboplastin generation. Our Cases IV, V and VI were all considered as secondary thrombocythæmia and all were found to have abnormally high platelet counts soon after hæmorrhage; their bleeding times were all normal.

Clinical distinction between primary and secondary types may be very difficult. Case III, for example, was noted to have thrombocythæmia soon after a severe hæmorrhage following dental extraction. The bleeding time was, however, abnormally prolonged (thirty-eight minutes) and the thromboplastic function of the platelets was poor. It may often be difficult to decide whether the hæmorrhage results from thrombocythæmia or is the cause.

The association between high platelet counts and poor platelet function could be explained in a number of ways. Are these platelets being formed so rapidly that they are deficient in some essential hæmostatic factor? It has been shown that these platelets are deficient in another factor, 5-hydroxytryptamine (serotonin), although the whole blood serotonin is not reduced owing to the thrombocythæmia. Alternatively is there some impairment in the mechanism for removing platelets so that there is an undue proportion of ageing platelets which are probably inefficient?

Stefanini and Dameshek (1953) established that transfused platelets only survive for a maximum period of four to five days. This is true even after splenectomy as has been shown by our department (Bell *et al.*, 1956). We have also demonstrated that platelets stored in siliconed containers for more than four to five days are ineffectual in arresting hæmorrhage in thrombocytopenia.

In our third case the thromboplastin-generation at the higher concentration of platelets was very poor and markedly less than at the 100,000/c.mm. level. It is interesting that Spaet, Bauer and Melamed (1956) have recorded an anticoagulant activity of platelets at high concentrations in a patient with hæmorrhagic thrombocythæmia by the thromboplastin-generation test. They also found anticoagulant activity of normal platelets when concentrated to thrombocythæmic levels.

The question of anticoagulant action of normal platelets at high concentrations should be pursued further as a possible cause of hæmorrhage.

The majority of authors who have described this condition consider that it is a form of myeloproliferation. Most cases have shown an increase in megakaryocytes in the bone-marrow with marked platelet budding. We found a moderate increase of megakaryocytes in Case III but have only studied the marrow ourselves in one other case (Case II) where the films unfortunately showed diminished cellularity, probably due to hæmodilution.

Abnormality of the spleen has been commented on by others; Epstein and Kretz (1930) and Fanger *et al.* (1954) have noted atrophy of the spleen associated with thrombocythæmia, whereas Rowlands and Vaizey (1938) and Owren (1943) noted splenomegaly.

In our cases, only 1 showed slight clinical enlargement of the spleen.

While the ætiology of the condition remains obscure, we consider that there is now sufficient evidence to recognize primary hæmorrhagic thrombocythæmia as an entity.

REFERENCES

BELL, A. D., MOLD, J. W., OLIVER, R. A. M., and SHAW, S. (1956) *Brit. med. J.*, ii, 692.
BIGGS, R., and DOUGLAS, A. S. (1953) *J. clin. Path.*, **6**, 23.
EPSTEIN, F., and KRETZ, J. (1930) *Klin. Wschr.*, **9**, 1177.
FANGER, H., CELLA, L. J., and LICHTMAN, H. (1954) *New Engl. J. Med.*, **250**, 456.
HARDISTY, R. M., and WOLFF, H. H. (1955) *Brit. J. Hæmat.*, **1**, 390.
JASINKI, B. (1949) *Acta hæmat.*, **2**, 145.
MACFARLANE, R. G., and BIGGS, R. (1955) *Med. Res. Counc. Memor.*, No. 32, 10.
OWREN, P. (1943) *Gastroenterologia, Basel*, **68**, 148.
PUDLÁK, P., HEŘMANSKÝ, F., and FIALA, J. (1955) *Čas. čes. Lék.*, **94**, 693.
REID, J. (1940) *Lancet*, ii, 584.
ROWLANDS, R. A., and VAIZEY, J. M. (1938) *Lancet*, ii, 1217.
SPAET, T. M., BAUER, S., and MELAMED, S. (1956) *Arch. intern. Med.*, **98**, 377.
STEFANINI, M., and DAMESHEK, W. (1953) *New Engl. J. Med.*, **248**, 797.

DISCUSSION

**Dr. R. M. Hardisty** said that Dr. Chanarin had shown that the rate of plasma clearance of folic acid was increased in cases of pernicious anæmia, but within normal limits in the anæmia associated with anticonvulsant drugs. He asked Dr. Chanarin to explain why he classed both these conditions as instances of the failure of utilization of folic acid and how these findings threw light on the interrelationship of folic acid and vitamin $B_{12}$.

He asked Dr. Shaw whether he regarded the results of his thromboplastin-generation tests on the platelets of the hæmorrhagic group as significantly different from the controls.

**Dr. G. I. C. Ingram,** on Dr. Shaw's paper, suggested that all the cases might have been examples of primary thrombocythæmia, with the possible exception of Case IV, in which the platelet count returned spontaneously to normal. From the clinical point of view, bleeding might have been associated with a pre-existing thrombocythæmia, rather than having caused a "secondary" rise in platelet count. In the thromboplastin generation test he had found that thrombocythæmia platelets could usually be shown to be more inhibitory than normal platelets when both were tested at concentrations over about $10^6$ per c.mm. The platelets from the 3 cases included in Fig. 4 might have been found to be more inhibitory than normal had they been tested at a concentration ten times higher.

**Dr. H. E. M. Kay** questioned Dr. Chanarin's interpretation of the folic acid absorption curves in the cases of megaloblastic anæmia of pregnancy and suggested that the low plasma levels were due to rapid clearance rather than defective absorption.

**Dr. D. D. Mollin,** in reply to a question, agreed that it was true that patients with megaloblastic anæmia due to anticonvulsants might respond to treatment with vitamin $B_{12}$, particularly if relatively large doses were given. In this they resembled some patients with megaloblastic anæmia of the puerperium. It was difficult to imagine why they did this. Occasionally, these patients might be vitamin-$B_{12}$-deficient (Kidd and Mollin, 1957). However, only 2 out of 20 patients, whose sera had been assayed, had subnormal serum vitamin $B_{12}$ levels, and hæmatological responses had been seen in patients whose serum $B_{12}$ levels, although low, were within the normal range (Badenoch, 1954).

Even when treatment with vitamin $B_{12}$ induced a remission in these patients, this was incomplete unless the anticonvulsant drug was also stopped. The hæmoglobin concentration might rise to within the normal range but there was residual macrocytosis and the marrow would still show intermediate megaloblastic change.

REFERENCES.—BADENOCH, J. (1954) *Proc. R. Soc. Med.*, **47**, 426. KIDD, P., and MOLLIN, D. L. (1957) *Brit. med. J.*, ii, 974.

**Dr. S. Shaw,** in reply to Dr. Ingram, pointed out that at the time when this work was being carried out the authors had not any information concerning the possible anticoagulant effect of platelets at high concentrations and that further tests using normal platelets and platelets from patients with primary and secondary thrombocythæmia would elucidate this point.

In reply to Dr. Hardisty, **Dr. Shaw** said that while the results of thromboplastin-generation tests in the secondary thrombocythæmic group were similar to those of the controls, he considered that thromboplastin-generation in the three cases of primary hæmorrhagic thrombocythæmia was significantly slower. It was interesting that the difference was greatest at the platelet concentration found in the blood, and in Case 3 which showed the most prolonged bleeding time.

**Dr. Chanarin,** in reply to Dr. Hardisty, said that although folic acid deficiency appeared to determine the development of anæmia in Addisonian pernicious anæmia, these patients did not respond well if at all, to small doses of folic acid, and only responded to large doses. If, as seems likely, a folic acid-like compound is the final "antimegaloblastic" substance, then in $B_{12}$ deficiency there must be some difficulty in either converting pteroylglutamic acid into this active form, or in maintaining it in that form. In this sense $B_{12}$ deficiency appeared to interfere with the utilization of folic acid.

The mode of action of the anticonvulsant drugs appeared more analogous to the action of the folic acid antagonists.

In reply to Dr. Kay, Dr. Chanarin said that the low serum folic acid levels found in the absorption tests in pregnancy were unlikely to be due to more rapid clearance of the absorbed folic acid from the plasma since all the patients were "saturated" with folic acid by giving them large doses of folic acid for four days before the test. A 24-hour gap was then allowed for the clearance of all folic acid from the plasma before an absorption test was performed. An increase in plasma volume in pregnancy, however, could contribute to some lowering of the serum levels when a standard dose of folic acid was used. The observations were therefore repeated in both pregnancy and control subjects using an oral dose of folic acid adjusted to body weight, and the original observations were confirmed.

# Section of Urology

President—LESLIE N. PYRAH, M.Sc., Ch.M., F.R.C.S.

[*March* 27, 1958]

## SYMPOSIUM ON LOWER THIRD OF URETER

**Professor G. Causey** (London): *The Anatomy of the Lower End of the Ureter*

In this short review of the structure of the lower end of the ureter I shall take only a few apparently isolated aspects in which there is, however, an immediate relation between the structural and developmental factors, and the pathological ones.

*The normal relationships of the ureter.*—The abdominal part of the ureter is, of course, vertical in the anatomical position of the subject, and the pelvic part passes downwards and forwards from the brim of the pelvis to the trigone with a gentle curve, with its concavity forward as the ureter accommodates itself to the backward curvature of the pelvic wall, and concave medially as the ureter accommodates itself to the lateral wall of the pelvis. The structures that are lying in immediate lateral relationship to the ureter on the lateral wall of the true pelvis are, from above downwards, the external iliac artery, the external iliac vein, the obturator nerve, the obturator artery and the obturator vein. As we come towards the anterior part of the pelvic ureter in the male the vas deferens, after hooking round the inferior epigastric branch of the external iliac artery, crosses over the ureter from the lateral to the medial side. If one removes the vas deferens from the picture and places an ovary and tube in the angle between the external and internal branches of the common iliac, and if one separates this ovary by a layer of peritoneum from the foregoing structures, then we have the immediate relationships of the ureter in the female pelvis.

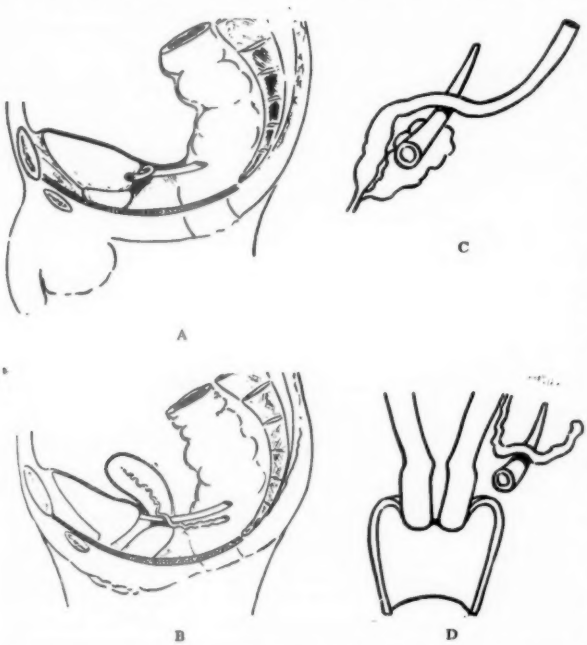



FIG. 1.—A and B, diagrammatic section of the male and female pelvis respectively. C, diagrammatic anterior view of the ureter, vas deferens and seminal vesicle. D, diagrammatic anterior view of the ureter and uterine artery at the side of the supra-vaginal cervix.

A more important practical relationship is that of the ureter to the seminal vesicle and the vas just at the base of the bladder in the male and to the supra-vaginal cervix and the uterine artery in the female. These two positions are in many ways comparable (Fig. 1). The vas is seen to be crossing the ureter from lateral to medial and is above the ureter; but as the ureter is descending rather acutely, the vas is also in front of the ureter and in the same way, the ureter, because it is going downwards as well as forwards is first of all above the tip of the seminal vesicle, and is thereafter, as it enters the bladder, well in front of the tip of the seminal vesicle. The lower diagram in Fig. 1 shows the relationship of the ureter to the lateral side of the supra-vaginal cervix, and again as the ureter is both

going forwards and downwards it will be related to the vaginal fornix in a similar way to its relation to the seminal vesicle in the male, that is, it is first of all running over the top of the fornix and then as it runs into the base of the bladder it is running downwards and medially in front of the anterior vaginal fornix. The relationship of the uterine artery to the ureter is in many ways similar to the relationship of the vas deferens; the uterine artery is above but also in front of the ureter and the relationship is not only close, but also extensive because of the slope of the ureter. The range given for the distance of the ureter from the supra-vaginal cervix is 1–4 cm. This in itself is rather a wide variation, but of course is nothing to the variation that can be found in many pathological conditions.

*The actual entry of the ureter into the bladder* is an interesting region in that:

(1) The ureters are 5 cm. apart as they enter the bladder wall, and 2½ cm. apart as they open into the bladder cavity.

(2) There is a sleeve of loose connective tissue around the ureter as it enters the bladder wall (Waldeyer's sheath) which has by some been connected with the adaptation of the ureteric orifices to variable bladder size.

(3) The longitudinal musculature of the ureter is continuous with the trigonal musculature. The whole ureter has a circular muscle coat, but the longitudinal coat appears to be incomplete over most of the upper part of the ureter, and it is only in the lower part of the ureter that we get a well-defined longitudinal muscle coat that is continuous with the most superficial muscle layer of the trigone of the bladder (Wesson, 1920). The triangular muscle sheet thus formed is more obvious at the edges than in the middle and the sweep of these longitudinal muscle fibres between the two ureteric orifices gives rise to an elevation in the mucous membrane called Mercier's bar. The other two sides of this muscular triangle form the two lateral bars of muscle called the muscle of Bell, which are continuous from the ureteric orifices as far as the internal meatus.

The stratified squamous epithelium of the ureter is continuous with that of the bladder and at the edges of the ureteric orifices this forms a double fold whose valvular function has been argued for many years.

*The blood supply* (Fig. 2).—Like most other elongated structures, there is a longitudinal anastomosis of the vessels along the ureter, and this longitudinal anastomosis is reinforced by small twigs from any and every vessel in the neighbourhood. On the right-hand side, the ureter is supplied from the common iliac and from the superior part of the hypogastric artery, and from the vesico-deferential artery, whereas on the left-hand side there is usually a branch direct from the aorta, and none from the common iliac. It is quite clear that there is interchangeability in these patterns, but I would stress that the vesico-deferential artery is a very constant branch, supplying as it does a large part of the trigone of the bladder, it also supplies the terminal part of the ureter. The vesico-deferential is the only constant branch of that group of arteries which are commonly known as the middle vesical.

*The nerve supply of the ureter.*—There is a continuous reinforcement throughout the length of the ureter by nerve fibres arising from the aortico-renal ganglion from the aortic plexus and from the hypogastric plexus in the pelvis. The hypogastric plexus, of course, becomes very intimately related to the lower end of the ureter as it spreads out in minute branches towards the base of the bladder. This innervation is rather what one would expect to find, but the unexpected is met with when we come to consider Wharton's (1932) conclusions that this innervation which we have just described is almost entirely sensory and can be stripped off the ureter without interfering with its muscular action.

*The development of the lower end of the ureter.*—The ureteric bud is an outgrowth from the caudal end of the mesonephric duct, and this ureteric bud is an organizer of the metanephric cap that will form the adult kidney. It is a process of absorption of the lower end of the mesonephric duct into the bladder wall, or perhaps we should call it at this stage the wall of the urogenital sinus, which gives rise to the position in the adult human, where the ureteric opening is at the supero-lateral corner of the part of the bladder wall that is developed from the mesonephric duct. The vasa deferentia will cross above and to the medial side of the ureter to open into the caudal end of the part of the bladder that is formed from the mesonephric duct, in other words into the prostatic urethra. A small diagram which Abbie produced in 1941 stresses the phylogenetic significance of these relationships in the female. Fig. 3 shows that in the monotreme there is an opening of the mesonephric duct and of the paramesonephric duct into a common cloaca; in the adult placenta the mesonephric duct has retained its attachment to the part of the urogenital sinus which has formed the bladder, and the Müllerian or paramesonephric duct has passed caudally between the two developing ureters to form the uterus and most of the vagina. In the marsupial, shown in the middle, we have the most curious distribution in which the cloaca is split up into medial and lateral vaginæ with a bicornuate uterus opening into the cephalic end of the tripartite vagina and the ureter passing between the middle and lateral vaginæ.

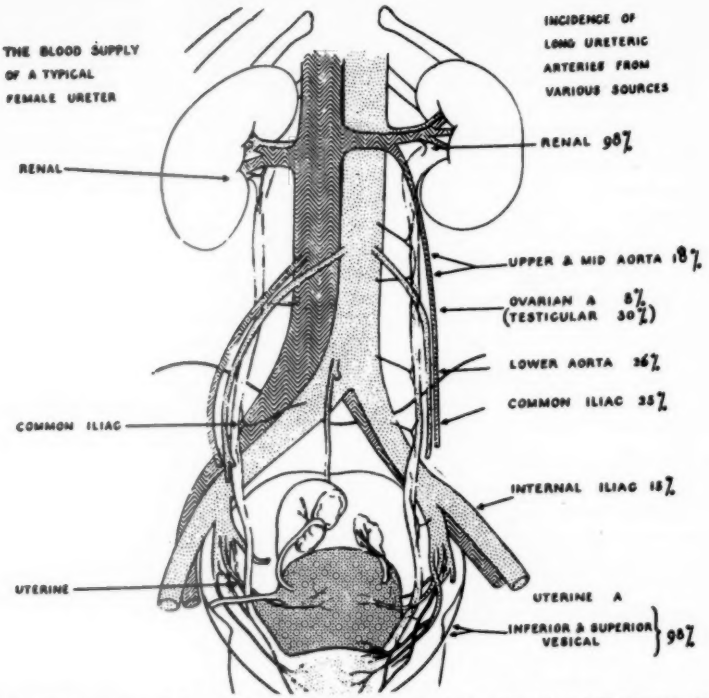



FIG. 2.—The sources of the arterial supply of the ureter (after Daniel and Shackman, 1952).

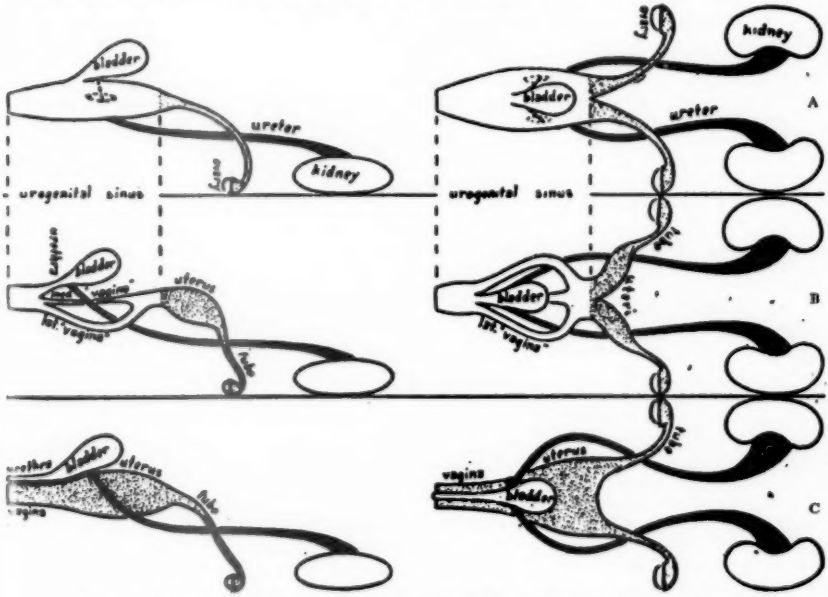



FIG. 3.—Schematic representation of the reproductive system in A, Monotreme; B, Marsupial; C, Eutherian (after Abbie, 1941).

The partition of the ureteric and mesonephric ducts and the absorption of the lower end of the mesonephric duct into the bladder wall give a very plausible explanation of the position of the aberrant openings in cases of multiple ureter. If we imagine two ureteric buds instead of one coming off the mesonephric duct, the upper going to what will be the upper pole of the adult kidney and the lower to the lower, then if these two buds are fairly widely separated as the mesonephric duct is absorbed, it is fairly clear that the lower ureteric bud will become attached to the bladder wall whilst the upper one is still attached to the mesonephric duct, and as differential growth proceeds the upper ureteric bud will be drawn down with the mesonephric duct towards the neck of the bladder and the final position of the secondary opening will be that the ureter from the upper part of the kidney will be more distal or caudal in its opening whether this opening be into the bladder, urethra or any other remnant of the cloaca. The sites of abnormal openings of the ureter have been collected by Hollinshead (1956). If the two ureteric buds are close together, then they will tend to be close together in the bladder wall; if they are widely separated, then we might expect a wide separation in their final positions. In the male pelvis the aberrant opening of the ureter from the upper part of the kidney tends to be towards the neck of the bladder or in the prostatic urethra, but there are cases into the rectum or seminal vesicals. All these openings are caudal to the normal ureteric orifice. In the female pelvis the openings are not only into the urethra but into the vestibule which represents the membranous urethra of the male.

REFERENCES

ABBIE, A. A. (1941) *Aust. J. Sci.*, **4**, 77.
DANIEL, O., and SHACKMAN, R. (1952) *Brit. J. Urol.*, **24**, 334.
HOLLINSHEAD, W. H. (1956) Anatomy for Surgeons. London; Vol. 2.
WESSON, M. B. (1920) *J. Urol.*, **4**, 279.
WHARTON, L. R. (1932) *J. Urol.*, **28**, 639.

**Mr. G. F. Murnaghan** (Institute of Urology, University of London, and the Department of Surgical Science, University of Edinburgh):

*The Physiology of Megaureter*

The factors which control the activity of the upper urinary tract are still not clearly understood. Many studies of the autonomic innervation of the ureter have not disproved the theory first postulated by Engelmann (1869) that the contractions of the ureter are myogenic and autonomous. It has been suggested by Lapides (1948) that the stretching of the muscle coat is the normal and adequate stimulus for the initiation and maintenance of these contractions, whilst Bozler (1938) considered that the contractile process is propagated through a syncytium of smooth muscle cells without the intervention of intrinsic nerves. It is therefore perhaps reasonable to attach functional significance to the movement patterns of isolated ureteric segments and in this paper I would like to compare the activity of the normal ureter with that of the megaureter as seen during perfusion under controlled conditions. The pig ureter has been found to behave in a similar manner to the human ureter and because it is easily obtained, it has been used during many experiments as the control. After perfusion the various segments have been examined histologically so that the arrangement of the muscle fibres in their walls could be correlated with the movement patterns previously observed.

The method of perfusion and the technique of selecting longitudinal sections for histological study have been fully described elsewhere (Murnaghan, 1957*a*, *b*). Their application has shown that a normal variation in muscular structure may be responsible for the different movement patterns observed during perfusion of the separate thirds of the ureter.

Schneider (1938) demonstrated that the bundles of muscle fibres in the wall of the ureter form a series of spirals and this arrangement has been verified by Carando and Dell'Adami (1950). There is apparently no uniformity in the distribution of these spirals throughout the length of the ureter and they must vary in their winding in order to explain the different disposition of the muscle bundles which can be seen in both longitudinal and transverse sections of the ureter at different levels. In the renal pelvis and middle third of the ureter the spirals form a predominantly circular muscle coat, but in the upper third and in the region of the pelvi-ureteric junction they are intermingled and the muscle bundles pass in all directions. Towards the lower end of the ureter they are apparently open and elongated so that the muscle fibres are predominantly longitudinal in disposition. Satani (1919) described this predominance of longitudinal muscle in the lower ureter and maintained that circular fibres were altogether absent from its intramural portion. He also noted that the thickness of the longitudinal layer decreased more rapidly on the medial than on the lateral side.

During perfusion at low pressures and at normal rates of flow, contractions usually begin where the circular fibres predominate, but the renal pelvis is the first portion to be stimulated

and as its rhythm is faster than that of the middle third of the ureter, it acts as the pacemaker during the perfusion of whole lengths. These low pressure contractions travel along the ureter in the form of waves—the so-called "iso-peristalsis", and they do not change their nature as they pass through the different patterns of spiral formation in the muscle coat.

When the distension pressure is raised, this variation in muscular structure apparently assumes important significance because the movement patterns of the separate thirds of the ureter become quite distinct. The ureter divides into spindles which in the isolated organ are usually three in number and are delineated by the dilatation of the pelvis and middle ureter, by the elongation of the lower ureter and by the reluctance of the upper ureter to increase either its girth or its length. It could be suggested that a different contractile process is now responsible for the activity of these spindles at high pressure. They do not await the arrival of a contraction wave which possibly depends upon the conduction of the excitation process along the muscle coat. The pressure within the individual spindle will be uniform and all the fibres in its wall will be subjected to stretch and could respond by a synchronous contraction which would involve the whole spindle simultaneously.

The direction of the fibres in the wall of the spindle will thus control the degree of dilatation or elongation, it will allow for possible differences in muscle tonus and may be responsible for the different rates of contractions in the separate spindles during perfusion at high pressure.

The upper spindle with its mixed muscle bundles prefers to conduct the contractions which arise in the pelvis and is reluctant to initiate its own response to distension. This behaviour may protect the renal pelvis from back pressure so that its circular muscle coat can continue as the pacemaker. Fluid is thus propelled into the middle spindle where the circular muscle coat facilitates dilatation but also produces a powerful contractile response to distension which causes a shut-down of the whole spindle and propels a large volume of fluid into the lower spindle. The lower ureter with its longitudinal muscle responds to distension by contractions which consist largely of shortening, and which discharge the fluid through the resistance to flow at the ureteric orifice or through any device incorporated in the perfusion circuit.

If the resistance to outflow prevents egress from the lower spindle, fluid apparently flows back into the middle spindle to produce progressive distension of both the middle and upper spindles. As the distension pressure rises the contractions of all three spindles become progressively weaker but the pattern of the contractions remains the same and though there may be a reversal of flow in the obstructed ureter, retrograde contractions have not been observed under these conditions when the whole of the lower spindle has been included in the preparation. During increasing distension the lower spindle is usually the last portion of the ureter to become completely inert.

The bladder trigone has been included in a few of the preparations and has been reconstituted to form a small bladder segment which was poorly contractile. It was connected to a manometer tube so that the tube itself really represented an inert bladder cavity.

Using this assembly as previously reported (Murnaghan, 1957*b*) it has been possible to demonstrate that the ureteric orifice may offer resistance to ureteric flow during perfusion. It is possible that this resistance is due to tonic contraction of the musculature of the isolated bladder around the intramural ureter. Though this resistance is usually negligible or very low, it has on occasion been as high as 15 cm. $H_2O$. At such perfusion pressures only the lower spindle of ureter is actively contractile, and it is interesting to note that the orifice opened only at the precise moment of contraction of the lower spindle even when the bladder pressure was lower than that of the ureter. It could be argued that the opening of the orifice was due to the pressure generated by the contraction, but it also seems reasonable to assume that unless the contraction of the lower spindle in some way reduced the resistance at the ureteric orifice, then the fluid would simply flow back into the middle spindle as previously described.

With increased bladder filling and the development of bladder tonus there will eventually develop hydrostatic opposition to egress from the lower ureter which is not dependent upon any resistance at the ureteric orifice. Even without reflux from the bladder, such opposition will lead to a failure of the lower spindle to empty and produce retrograde flow in the ureter and distension of the upper ureter and renal pelvis.

Gruber (1929) demonstrated that the intravesical, as distinct from the intramural ureter, acts as a true valve which does not allow reflux from the bladder. He showed that the flap of this valve in both man and pig could be as long as 26 mm. and contained longitudinal muscle fibres from the ureter. Further extension of the longitudinal ureteric muscle along the edges of the bladder trigone was described by Bell (1816) and his findings were verified by Ellis (1856) and by Wesson (1920). Learmonth (1931) demonstrated that stimulation of the vesical sympathetic nerves produced simultaneous contraction of the trigone and closure of the ureteric orifices, but he considered that the control of these two structures was to some extent dissociated.

The shortening of the longitudinal muscle of the lower ureter might well make an important

contribution to the opening of the ureteric orifice by elevating and shortening the flap of the valve formed by the intravesical ureter, whilst the unequal distribution of these long fibres may help to undo the obliquity of the intramural ureter.

From these observations it appears that the longitudinal disposition of muscle fibres in the lower ureter is particularly suited to the task of propelling urine through the orifice into the bladder. The lower spindle is reluctant to initiate retrograde contractions but continues to contract even at the highest pressures; its shortening may be largely responsible for the opening of the orifice and the absence of circular muscle fibres from its wall enables it to contract without undue diminution of its calibre and with the minimum amount of resistance to ureteric flow.

*Megaureter*

The specimens were obtained from patients admitted to the Hospital for Sick Children under the care of Mr. D. Innes Williams who considered that a diagnosis of megaureter was justified by the failure to demonstrate any organic obstruction at the ureteric orifice or in the lower urinary tract to account for the ureteric dilatation which was unilateral.



FIG. 1.—Retrograde pyelogram of unilateral megaureter.

The type of case is illustrated by the retrograde pyelogram shown in Fig. 1. The ureteric catheter is still *in situ* and the ease with which such a catheter could be passed through an orifice of normal appearance was accepted as reasonable evidence that there was no true stricture at the lower end of the ureter. It is interesting to see that the dilatation of the renal pelvis is not perhaps as advanced as that of the lower ureter. From this pyelogram it is not possible to determine the exact calibre of the upper ureter which might well have been contracting at the moment of exposure. This megaureter presented in a 3-year-old boy who was subjected to nephro-ureterectomy after which the kidney and ureteric orifice were detached from the specimen but preserved for histological examination. The renal pelvis, and practically the whole length of ureter, were then perfused under precisely the same conditions as the normal human or pig ureter, with the inflow at the renal end of the specimen. At low pressures contraction waves began most frequently at the lower end of the megaureter and travelled in a retrograde manner along its whole length and across the renal pelvis. With a slight elevation of perfusion pressure, some contractions began in the pelvis and passed through the junction and along the upper ureter in a normal manner. When they encountered the abnormal contractions from the lower end, both contractions merged and proceeded back into the renal pelvis. As the distension pressure was raised even further it was noted that the upper spindle and not the lower spindle of this ureter was the last segment to become inert at a pressure of 80 cm. $H_2O$.

On histological examination it was found that the muscle coat of the whole length of ureter was greatly hypertrophied and all three spindles were composed of predominantly circular muscle. The renal pelvis and pelvi-ureteric junction showed a normal arrangement of their muscle fibres and the usual transition into more longitudinal fibres was beginning at the junction of the middle and lower spindles. This transition was, however, incomplete and in the lower spindle itself the fibres became more definitely circular in arrangement as the lower end of the ureter was approached. This predominance of circular muscle in place of the usual longitudinal bundles was also found in the intramural portion of this ureter.

A similar specimen was obtained from a 3-year-old girl. During perfusion the contractions showed the same preference to begin at the lower end of the ureter, though occasional normal contractions began in the renal pelvis. On this occasion all three spindles became inert at the same time and at a distension pressure of 47 cm. of water. Histological examination again revealed hypertrophy of the whole ureter with an unusual predominance of circular muscle in the three spindles but particularly in the lower spindle. The fibres of the intramural ureter passed in all directions but showed a marked tendency to be circular rather than longitudinal.

From the histological point of view it is interesting to note how the appearances of longitudinal sections of the lower spindle of megaureter closely resemble those of the hypertrophied pelvis of congenital hydronephrosis. When reviewed in the light of the normal movement patterns and normal muscle structure, it would seem reasonable to attribute the origin of the retrograde contractions of these megaureters to the preponderance of circular

muscle at their lower ends. Such retrograde contractions are quite distinct from the back-flow which occurs in the obstructed ureter and have in fact been visualized by Edwards (1957) during his clinical investigation of megaureter by cine-ureterography.

The presence of circular muscle in its intramural portion might cause the megaureter to close the ureteric orifice rather than to open it as its lower end contracts. This unusual muscular arrangement has been found in a case of congenital stenosis of the ureteric orifice, the lumen of which would admit only a stout bristle.

I have not had the opportunity of perfusing a megaureter with a supravesical narrow segment but the histological appearances of the muscle coat in the lower end of one such ureter were abnormal. At the level at which the lumen narrowed there was a slight reduction in the degree of hypertrophy but no change in the unusual and circular direction of the muscle fibres.

When retrograde contractions are persistently present in the ureter the propulsive efficiency of the whole system must be greatly impaired. There will be a demand for increased work to which the ureter will respond by dilating—it was emphasized by Begg (1946) that ureteric dilatation, in the first instance, is a physiological and active adaptation by the smooth muscle coat in order to increase its efficiency. As time goes by this mechanism of compensatory dilatation is enhanced by muscular hypertrophy and these megaureters are strongly contractile until fatigue is induced or aggravated by infection.

If there is an abnormal preponderance of circular muscle in the intramural ureter such fatigue might allow for undue relaxation of its lower end and produce gaping of the orifice with reflux from an otherwise normal bladder.

The problem is therefore to establish whether the preponderance of circular muscle at the lower end of the megaureter constitutes the primary abnormality and the true cause of the increased sensitivity of the lower spindle. It must be decided whether this unusual muscular distribution is not in fact a selective hypertrophy of the circular element of the muscle spirals secondary to some other intrinsic defect at the uretero-vesical junction.

The histological appearances of the lower ends of dilated ureters, secondary to urethral obstruction, were studied by Kretschmer and Hibbs (1933). In those cases of their series which could clinically be described as hydroureters as distinct from megaureters, there was hypertrophy of the muscle coat and most of this hypertrophy involved the longitudinal fibres. It has been possible to demonstrate this pattern in one of my own specimens removed from a 5-year-old boy with anterior urethral valves but this ureter was unfortunately inert on perfusion.

Before the anatomical basis for these observations can assume its proper perspective it will be necessary to establish in terms of absolute and relative length the exact distribution of longitudinal muscle at the lower end of the healthy ureter in the fœtus and in early infancy. It is unlikely that such specimens will ever be available for perfusion in a physiological bath and at this stage the problem might well be referred to the histologist.

Meantime, it is suggested that the dilatation of the megaureter is the result of abnormal ureteric contractions which may be due to a predominance of circular muscle in place of the usual longitudinal muscle at the lower end of the ureter, and is possibly aggravated by a failure of the normal opening mechanism of the ureteric orifice as the result of the extension of circular muscle into its intramural portion.

I wish to thank the Director and Staff of the Institute of Urology, where most of this work has been done. I am most grateful to Mr. D. Innes Williams for the supply of material, and to Dr. R. C. B. Pugh for his help with the histological studies.

In the University of Edinburgh this research programme has been supported by a grant from the Scottish Hospital Endowments Research Trust.

## REFERENCES

BEGG, R. CAMPBELL (1946) *Brit. J. Urol.*, **18**, 176.
BELL, C. (1816) *Med.-chir. Trans.*, **3**, 171.
HOZLER, E. (1938) *Amer. J. Physiol.*, **122**, 614.
CARANDO, M., and DELL'ADAMI, G. (1950) *Arch. ital. Urol.*, **24**, 137.
EDWARDS, D. (1957) *Brit. J. Urol.*, **29**, 410.
ELLIS, G. V. (1856) *Med.-chir. Trans.*, **39**, 327.
ENGELMANN, T. W. (1869) *Pflügers Arch. ges. Physiol.*, **2**, 243.
GRUBER. C. M. (1929) *J. Urol.*, **21**, 567.
KRETSCHMER, H. L., and HIBBS, W. C. (1933) *Surg. Gynec. Obstet.*, **57**, 170.
LAPIDES, J. (1948) *J. Urol.*, **59**, 501.
LEARMONTH, J. R. (1931) *Brain*, **54**, 147.
MURNAGHAN, G. F. (1957*a*) *J. Physiol.*, **135**, 32P.
—— (1957*b*) *Brit. J. Urol.*, **29**, 403.
SATANI, Y. (1919) *J. Urol.*, **3**, 247.
SCHNEIDER, W. (1938) *Z. ges. Anat.*, **109**, 187.
VESSON, M. B. (1920) *J. Urol.*, **4**, 279.

**Mr. Howard G. Hanley** (London):

*The Lower Ureter in Tuberculosis [Abridged]*

A very common radiological finding in patients with early bladder symptoms in genito-urinary tuberculosis is a constant filling of the lower ureter, with or without some degree of dilatation. This phenomenon is also seen in young women with non-specific cysto-urethritis and much more markedly so in association with the typical cystoscopic changes of abacterial pyuria.

When these changes are due to bladder or urethral irritation they are reversible and return to normal when the bladder lesion heals, even if it be tuberculous. However, if the ureter itself is involved, as it frequently is in tuberculosis, the dilatation may be permanent and progressive.

The two most important permanent changes to be on the lookout for are therefore true stricture formation and ureteric reflux.

*Stricture.*—The problem of the ureteric stricture is I believe now well on the way to being solved, though much more work and observation will be required before the best operative techniques can be generally agreed upon.

A stricture at the lower end of the ureter is no longer an indication for nephro-ureterectomy. The ideal procedure is excision of the stricture and re-implantation of the ureter into the bladder. Although we have observed many tuberculous distortions of the upper and middle portions of the ureter under the X-ray amplifier, we have not yet encountered a true stricture in these regions which came any way near to obliterating the lumen. This is not to say that it does not occur, but in general, strictures are found in the lower third and usually just above the intra-vesical portion of the ureter. This is most fortunate since re-implantation is usually possible.

Inability to pass a ureteric catheter on one or more occasions does not necessarily indicate a stricture, as many of the rigid and irregular orifices which will not admit a catheter do frequently permit reflux from the bladder. A cystogram is therefore essential before contemplating ureteric re-implantation. If reflux is present re-implantation may make the condition worse, especially if the bladder is involved.

It is also essential that re-implantation should not be carried out in the presence of an active tuberculous cystitis. Cystitis generally responds rapidly to anti-tuberculous drugs, and re-implantation can be considered after three to four months' treatment. On only one occasion was my hand forced. This was a patient with a very high blood urea due to a solitary kidney obstructed at the ureteric orifice. In this instance I did an immediate nephrostomy, and followed this by a ureteric re-implantation after four months' drug treatment.

One difficult point is, when to decide to re-implant the ureter. We have watched several cases over the years and some of them have become no worse radiologically—but they still have dilated ureters. We have re-implanted eleven ureters out of approximately two hundred cases in nearly four years. I feel we should have done more—but it is always tempting to leave well alone for the time being.

The ideal technique of re-implantation would be to create a valvular orifice which would limit reflux, but many of the operations devised to achieve this end are not really applicable to the tuberculous case. In megaureter, &c., there may be no periureteritis whatever—but in tuberculosis there is, and my attempts to pull the ureter down through an intra-vesical approach, let alone fold it back in the form of a cuff, have been disappointing, and I have generally had to explore the ureter extra-vesically as well; in fact a Boari type of flap operation planned as such from the start has been quicker and more effective.

Though technically this operation presents no great difficulty the morbidity can be high. We are operating upon a ureter from a kidney which is " on the brink ", so to speak, and in most of our cases the kidney has been secondarily infected owing to obstruction before we started. We have had fistulæ and prolonged pyrexia—but in all cases the end-result has been satisfactory (Fig. 1).

*Reflux.*—In tuberculosis we are confronted with the worst type of reflux, which may occur from a systolic bladder up the ureter of a possibly uninfected or healed solitary kidney, and we have found that cystograms are of very great value in the assessment of such cases. (Illustrated by cine cystograms.)

An ileocystoplasty can afford symptomatic relief for the patient and functional relief for the kidney and should probably be performed more often. I favour patch operations to closed loops where possible, and would refer to the very high degree of adaptation which occurs in tuberculous patients. They become progressively more comfortable; they learn to empty the bladder by double or even treble micturition, while mucus in the urine tends to disappear. This is in direct contrast to some of the Hunner's ulcer patients, where the initial results of an ileocystoplasty are good, but are not always maintained.



A B

FIG. 1.—A (24.6.57), Tuberculous stricture at lower end of right ureter. B (4.10.57), Same case four months after ureteric re-implantation using Boari flap technique.

We have observed many of our ileocystoplasty cases under the X-ray amplifier, and the views expressed at Liverpool three years ago still hold good (Hanley, 1956, *Brit. J. Urol.*, **28**, 402). Radiologically, the flap operations empty much more efficiently than the loop operations which tend to hold a relatively large volume of residual urine, especially in a distal loop. In some cases, however, the patient may not be aware of this, and from his point of view the operation may be a complete success. Nevertheless, there appears to be much less ureteric reflux in the patients who do not retain a large volume of urine in the loops.

So far we have only considered the patient with the contracted bladder and perhaps a wide open ureteric orifice, but reflux may commence many years before this stage is reached, and we should always be on the lookout for its development. Unfortunately reflux is not always easy to detect and it may be only a transitory phenomenon in the early stages.

For the past few years we have been performing cystograms upon any of our tuberculous cases showing dilatation of the lower ureters. In the presence of an active cystitis reflux is common (perhaps up both sides—even the suspected normal side). In the majority of cases the reflux ceases when the bladder heals.

Now I would like to stress the importance of this point—the variability of reflux through an apparently normal ureteric orifice, and this is by no means confined to tuberculous patients. My attention was first forcibly concentrated upon this subject when I noted on the amplifier screen that during a certain retrograde pyelogram, reflux was occurring up an apparently normal ureter on the opposite side. The opaque medium was escaping from the pyelogram side into a half-empty bladder and was ebbing and flowing in irregular waves into and out of the opposite ureter. As always happens in such moments—the amplifier cine-camera was not loaded. The patient was therefore brought back for a film record a few days later—by which time, no trick which we could play would induce reflux up this ureter.

We have been able to verify this phenomenon on two occasions since then. Two young women recovering from acute pyelitis were due for catheter specimens of urine. Instead of these being done in the ward, they were performed on the X-ray amplifier table. A fine catheter was used to collect the specimen and empty the bladder, after which 80 c.c. of dilute Pyelectan solution were injected slowly with a Riches syringe. Immediate reflux occurred up the right ureter—the side of the pyelitis.

These women were reviewed approximately two months later, but reflux did not occur—even during micturition. These three examples prove or explain nothing, but they do pose many questions. Do we still have to cling on to the unlikely story of a blood-borne infection as a cause of pyelitis following a cysto-urethritis? Is reflux more likely to occur up the right side and does this account for the predominance of pyelitis on the right side, especially in pregnancy?

It should be possible to answer some of these questions without any difficulty, but we are up against a moral problem of academic curiosity versus "the best for the patient"—because I am now more than ever convinced that urethral instrumentation of any sort, even catheterization, should be avoided during an acute cysto-urethritis. It is easy to see why a pyelitis not infrequently follows such a procedure.

**Mr. F. P. Raper** (Leeds): *Ureterocele in Adults*

This paper reviews 50 cases of ureterocele. Such a number was obtainable only because Mr. J. C. Anderson in Sheffield, and Mr. Hamilton Stewart in Bradford, kindly allowed the author to review the records of their patients, and to include them with similar patients seen

in Leeds. Almost all were seen during the last ten years which means that any unit dealing mainly with urological disease will see about two patients with ureterocele each year.

*Sex.*—23 male and 27 female.

*Age.*—The ages ranged from 2 years to 79 years, and the most gross examples of the disease were found in the youngest people. Of greater interest is the fact that in this series of 50 patients only 3 were below the age of 5 and 2 in their teens. In other words about one ureterocele in 10 seems to be found in children.

*Side.*—In 7 patients the ureteroceles were bilateral, in 21 on the right and in 22 on the left.

*Type of ureterocele.*—The broad division into ureteroceles with an ectopic orifice and adult or simple ureterocele with an orifice in the normal position was suggested by Ericsson in 1954, and is a very useful subdivision. All the ureteroceles discussed in this paper are simple with an orifice in the normal position. If a further classification of them into size is of interest this can be done by taking one of the patients who had a large stone firmly impacted in the ureterocele which measured 2·6 cm. in diameter, and was the largest stone in this series. 43 patients in this series of 50 had ureteroceles definitely smaller than this, and only 6 had larger cysts.

*Stone and ureterocele.*—In this series 10 patients had stones actually lying in the ureterocele, and 2 had calculi in the kidney above the ureterocele. It may be that some of these patients had, in fact, a stone impacted at the orifice of a normal ureter rather than a stone impacted in a ureterocele, for it is well known that a stone lying for any length of time in one position in a ureter may cause dilatation of that area. The cystoscopic appearance, however, is very similar to that of a simple ureterocele, and the treatment is not affected by the presence of a stone.

*Symptoms.*—These are often multiple, but they tend to fall into well-defined groups. (1) Most commonly there were short attacks of loin pain often called renal colic. (17 patients.) (2) Attacks of urinary tract infection with fever. (11 cases.) (3) Hæmaturia. (9 cases.) (4) The ureterocele was an incidental finding. (8 cases.) (5) Difficulty in micturition due to prolapse of the ureterocele down the urethra. (2 cases.) (6) Pain in the R.I.F., urethra, epididymis. One of each.

*Radiography.*—The excretory pyelogram frequently reveals the diagnosis, sometimes by the appearance of the so-called halo effect. In other cases there is delayed emptying of the ureter. There may be a filling defect in the cystogram. In these patients dilatation of the upper urinary tract was present in 20 patients 4 of whom also had stones in their ureteroceles. In only 3 patients was there reduplication of the ureters on the same side as the ureterocele. One patient had bilateral hypoplastic kidneys.

*Treatment.*—It has been suggested that a ureterocele may not require any treatment, and in this series 6 patients have had no treatment for the condition. Of these 6 one has been followed for four years without any change in the ureterocele, and no change in his original symptom which was nocturnal enuresis. Another with bilateral ureteroceles has had only one treated, and the other has been watched for ten years, during which time it has been symptomless and has remained the same size. One patient has been watched for two years without any change in the condition. It therefore seems that if the ureterocele is not causing symptoms there is no particular reason why it should be treated by enlarging its orifice. The alleged danger of incising the orifice is that a minor degree of obstruction may be replaced by a major degree of ureteric reflux. 22 patients in this series have had the ureterocele treated by incision either with a diathermy electrode or with a meatotome. 7 patients who also had stones in the ureterocele have had the same treatment, but, in addition, the stone has been either removed at operation, or crushed and removed. 4 patients treated by incision of the ureterocele have had post-operative cystograms, and in none of these patients was there any reflux of the ureter although in one of them there was a moderate degree of hydronephrosis at the time when the ureterocele was treated. Symptomatically the results of treatment in these patients have been good in all but 8 patients who continued to get attacks of pain in the loin after the ureterocele had apparently been adequately incised. In 2 patients the pain eventually disappeared about two years after operation, but in the remaining 6 there was still a tendency to get pain. In 2 of these 6 there was gross renal damage, and 1 of these patients has since had a nephrectomy. 5 patients, 3 of them children, have had a nephro-ureterectomy because at the time the diagnosis was made they had obvious gross renal damage. 4 of these patients have done well, but 1 is now getting increasing dilatation of the lower half of a double kidney on the opposite side. 5 patients had open excision of the ureterocele the cut edges of the ureter then being stitched to the bladder wall in 2 places, and all these patients did well even though all of them had some degree of hydronephrosis before the operation. 2 patients were treated by dilatation of the orifice with ureteric catheters, and this appears to have relieved their symptoms.

REFERENCE.—Ericsson, N. O. (1954) *Acta chir. scand.*, Suppl. 197.

**Mr. D. Innes Williams** (London):

*Ectopic Ureterocele*

The term "ectopic ureterocele" denotes the intravesical protrusion which is made by the dilated lower end of ureter with a termination in the urethra. Strictly speaking, it is the ureteric orifice which is ectopic, while the protrusion itself is on the trigone but has several points of distinction from the simple ureterocele. The lesion is not clearly defined in earlier urological literature, being confused with cysts of the trigone and even with double bladder, but it was the subject of an excellent thesis by Ericsson in 1954. I have seen 22 examples, and it is upon these that the following description is based.

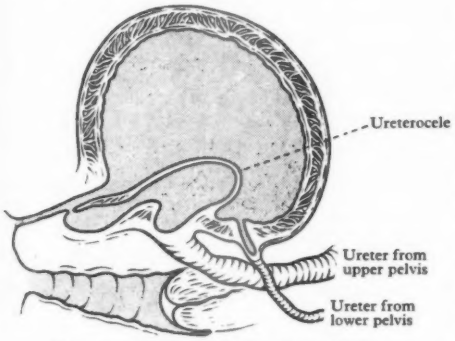



FIG. 1.—Anatomy of ectopic ureterocele.

The anatomy is shown in Fig. 1. The ectopic ureter is almost always derived from the upper pelvis of a double kidney and is dilated throughout its length. It passes through the muscular coat of the bladder a little below its fellow and then forms a wide ureterocele-like protrusion, but retains its own mucous membrane and muscularis distinct from the bladder mucosa. Somewhere about the level of the bladder neck it often narrows down and passes through the muscle tissue of the internal sphincter, though it may remain wider and more superficial, continuing the protrusion and down into the urethra. The actual ureteric orifice in the urethra is often wide and easily admits a catheter, but occasionally it is narrow or even completely occluded, and defies discovery. The opening lies above the verumontanum in the male, but anywhere in the urethra in the female or even externally in the vestibule. Between the simple ectopic ureter and the ectopic ureter with ureterocele, there are a few intermediate cases in which the terminal dilatation bulges a little into the bladder but is mostly extra-vesical.

The smaller ureteroceles lie at the bladder neck which may be mildly obstructed but the larger ones involve the whole trigone or even more of the posterior wall of the bladder: the second ipsilateral ureter, and the contralateral ureter are then drawn up on to the slopes of the protrusion and are themselves obstructed. Thus upper tract dilatation may not be confined to the ureterocele-bearing ureter; moreover, bilateral ectopic ureteroceles, perhaps fused in one large protrusion, also occur, and in some cases renal failure is already advanced when the child is first seen.

Ectopic ureterocele usually interferes considerably with the normal mechanics of the urinary tract and cases therefore present early in life, often during the first year. Urinary infection draws attention to the condition in the majority: a persistent pyuria causing a steady drain on the child's health, with exacerbations at times, perhaps even with a *B. coli* septicæmia. Acute retention of urine may occur, but more often it is chronic, with a dribbling overflow. The diagnosis of chronic retention is questionable, however, since the ureterocele itself may produce a swelling in the bladder large enough to be palpable in the abdomen and may be mistaken for residual urine. Incontinence may be due to retention, to chronic pyuria or to the ectopic termination of the ureter. One infant had two single ureters, one with ureterocele, but both ectopic so that no urine entered the bladder at all.

Prolapse of the ureterocele occurs in girls, either intermittently because a narrow based swelling is pushed down on its stalk through the urethra, or chronically because the ureterocele involves the entire length of the urethral wall down to the ectopic termination in the vestibule.

Abdominal pain may be due to acute obstruction of the ureterocele-bearing ureter which has sometimes been enormously dilated and kinked, producing a palpable mass in the abdomen which has something of the feel of an intussusception.

The diagnosis can almost always be made from intravenous pyelograms, but it must be recalled that the ureterocele-bearing ureter is derived from a non-functioning renal element which will not concentrate the opaque medium and its presence must be surmised from the characteristic deformation of the pyelogram and cystogram.

In the usual case with double ureter, therefore, the only pyelogram on the affected side is that of the lower pelvis, which differs from the normal in having its upper pole displaced laterally; in having a missing calyx or shortened upper infundibulum; in having a ureter

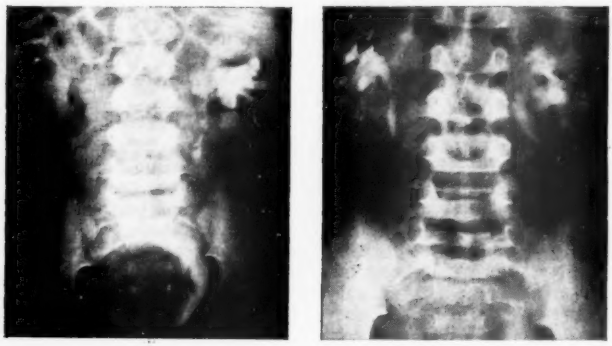


FIG. 2.—Ectopic ureterocele. Intravenous pyelogram showing the duplication of the right renal pelvis, and the filling defect in the bladder corresponding to the ureterocele. Girl aged 3 years.

which slopes gradually towards the paravertebral region instead of descending vertically; in having, in fact, all those indefinable features of countenance by which we recognize our acquaintances. It is, however, often hydronephrotic as well and the ureter shows signs of being displaced and indented by its companion, which is unseen, but even more dilated.

In the bladder, the smaller ectopic ureterocele appears as a filling defect almost in the mid-line at the bladder neck, its outline only a little more than a semicircle. The larger ones are higher, more lateral and more nearly circular, but are still based on the bladder neck in contrast to the simple ureterocele (Fig. 2). In extreme cases, the bladder shadow is represented only by a thin crescent of opaque medium around the circumference.

Endoscopic diagnosis is a far more difficult matter. A very large ureterocele obscures the entire cystoscopic field and it is only possible to say that there is a mass on the bladder base. A very small ureterocele is almost pedunculated, and being pushed to one side, may be overlooked when using a right-angled telescope. On urethroscopy, however, the nature of the protrusion is more easily seen, even if in some cases the ectopic ureteric orifice cannot be found. There is very little place for reconstructive surgery in the management of ectopic ureterocele: the corresponding renal element is small and damaged and will not repay preservation. Heminephrectomy with complete excision of the ureterocele-bearing ureter is therefore the treatment of the upper urinary tract. In the bladder, simple opening of the ureterocele is insufficient: it should be uncapped, removing the protrusion and suturing the bladder mucosa to the ureteric mucosa so as to leave a flat surface. Following this procedure the remaining ipsilateral and contralateral ureters will often return to normal if they have been dilated, and there is then a very good prognosis (Fig. 3A and B). However, the



A B

FIG. 3.—Ectopic ureterocele. Pre-operative pyelogram (A) in a boy aged 1 year with retention of urine shows bilateral hydronephrosis and a filling defect in the bladder due to bilateral ectopic ureteroceles on the ureters from the upper pelves. Post-operative pyelogram (B) shows the improvement after uncapping the ureteroceles and bilateral heminephrectomy.

dilatation is sometimes too far advanced and both renal elements on the affected side are severely damaged, so that total nephrectomy is better than heminephrectomy.

Where the ureterocele bulge continues well down into the urethra, and the ureter does not narrow at the level of the bladder neck, there is a danger that simple uncapping will leave a valve-like flap in the urethra. It is then wiser, although tiresome, to dissect out the ureter beneath the vesical mucosa and completely remove or tie off the lower extremity.

## REFERENCE

ERICSSON, N. O. (1954) *Acta chir. scand.*, Suppl. 197.

## BOOK REVIEWS

**The Extra Pharmacopœia (Martindale).** Vol. 1; 24th ed. (Pp. xxx + 1695. 65s.) London: The Pharmaceutical Press. 1958.

This latest edition hardly needs reviewing. The general arrangement is as usual, deletions have been few, and much new information has been added. The necessary changes relevant to the 1958 B.P. are indicated. The special sections on antibiotics, immunological products, and radioactive isotopes give a wide range of new and useful information. The editors and contributors are to be congratulated on their handling of such a mass of information, new and old. Criticism of detail is supererogatory: Martindale still continues to be a "must".

**Therapeutic Heat.** Ed.: Sidney Licht, M.D. Vol. II of Physical Medicine Library. (Pp. xiii + 466; illustrated. $12.00.) New Haven, Connecticut: Elizabeth Licht. 1958.

This book about heat covers all aspects of the problem, including theoretical physics, thermometry, physiology, clinical research and clinical application. There are twenty-three contributors, all experts in their own field.

As a collection of essays bringing together the known facts about this subject, it has no equal; and it is certain to become a standard reference book for physical medicine specialists and others wanting detailed information. Current research on the clinical application of heat is causing rapidly changing thoughts on the subject. At this stage, dogmatic statements might be misleading, and, therefore, this book is a discussion of research findings, rather than a quick guide to correct treatment.

Every chapter poses problems that have yet to be solved. The most important problem is the mechanism by which heat relieves pain. Although most workers have assumed that this is due to changes in tissue temperature and blood flow, they are reminded that the soothing effect of heat may be entirely due to impulses from the skin thermo-receptors interfering with the central reception of pain impulses. If this is so, the theoretical basis for deep heating is weakened still farther.

**Reflexogenic Areas of the Cardiovascular System.** By C. Heymans, M.D., and E. Neil, M.D., D.Sc. (Pp. viii + 271; illustrated. 56s.) London: J. & A. Churchill Ltd. 1958.

This book, which is well illustrated, describes the arterial baroreceptors and the chemoreceptors, and for the most part is concerned with the physiology of the cardiovascular reflexes. It outlines the pathways of the baroreceptor reflexes, and their general effects in the control of the circulation. It also explains how the cardiovascular reflexes of the carotid and aortic chemoreceptor areas are stimulated by anoxia, hypercapnia and by acidosis.

No teacher of physiology should be without this informative work on the subject.

**Safety Techniques for Radioactive Tracers.** By J. C. Boursnell, Ph.D., A.R.C.S., F.R.I.C. (Pp. xii + 68; illustrated. 7s. 6d.) Cambridge: Cambridge University Press. 1958.

Dr. Boursnell's small book should fill a gap on the bookshelves of many workers concerned with the use of radioactive tracers. Much of the subject matter was first presented as a committee report to the University of Cambridge.

In addition to the author's own advice, we have, collected in one volume, data formerly available only from reports of various official bodies. There is also a fairly complete bibliography.

The recommendations will be clear to anyone unfamiliar with the use of radioactive tracers and although the reviewer is aware that some of the procedures advocated approach a perfection which has not always been attained, it is agreeable to think that this book will help to eliminate hazards both to personnel and to results in the future.

**Studies on Phagocytic Stimulation.** By B. Gözsy, D.Pharm., D.Biochem., and L. Kátó, M.D. (Pp. 135.) Montreal: Institute of Microbiology and Hygiene of the University of Montreal. 1957.

This monograph is an informed account of the factors which bring about an inflammatory response, and the activity of the reticulo-endothelial system which results. It is brief,

up to date, and orientated in the direction of a chemical basis for the well-known morphological phenomena of inflammation. In translation from the original French a number of errors of grammar and spelling have resulted, and some of the chemical nomenclature is confused. The book ends with a useful list of 200 references, and would be of value both to the specialist in this field and to the general reader.

**Modern Trends in Endocrinology.** Ed.: H. Gardiner-Hill, M.D., F.R.C.P. (Pp. ix + 298 + 13; illustrated. 65s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

This compilation of essays is a gallant attempt to present every aspect of modern endocrinology. The individual contributions are well written, authoritative and adequately documented but the book fails because too many contributors have been allotted too little space to discuss too many subjects. Excellent as some of these factual snippets are, they do not penetrate deeply enough into the subject to provide a proper review of endocrinology.

The text is reasonably up to date but it is astonishing to find no mention of autoimmunization in thyroid disease or human intersex in the light of nuclear sexing.

The book is beautifully produced but expensive for a publication that will require another edition in a short while if it is going to record modern trends.

**Biochemical Investigations in Diagnosis and Treatment.** By John D. N. Nabarro, M.D., F.R.C.P. 2nd ed. (Pp. xi + 299. 25s.) London: H. K. Lewis & Co. Ltd. 1958.

The many admirers of Dr. Nabarro's book will welcome this second edition. The text has been brought up to date with a careful selection of recent advances and without upsetting the original balanced account of metabolic disturbances in disease and the relevant diagnostic methods. The sections on electrolytes and on the adrenal are particularly valuable.

This book should be read by all who are concerned with planning biochemical investigations. If the author's practical advice is followed by clinicians, the laboratories will not be burdened by inessential work.

**Rheumatoid Arthritis. A Definition of the Disease and a Clinical Description Based on a Numerical Study of 293 Patients and Controls.** By Charles L. Short, M.D., Walter Bauer, M.D., and William E. Reynolds, M.D. (Pp. x + 480; illustrated. 55s.) Harvard University Press. London: Oxford University Press. 1957.

This outstanding work is based on the long-term study of 293 consecutive patients with rheumatoid arthritis admitted to the medical wards of the Massachusetts General Hospital between 1930 and 1936, and treated by simple medical and orthopædic measures. 293 non-rheumatic subjects of the same age and sex were studied as controls. Patients were selected only if they fulfilled certain rigid criteria. These criteria, together with the differential diagnosis of rheumatoid arthritis, are discussed at length in one of the most interesting chapters of the book.

The study is divided into two parts: (1) a cross-sectional study of the disease in which are listed factors preceding and associated with the onset, and the type of course prior to hospital admission, and (2) a long-term follow-up, patients being reassessed first in 1937 and subsequently in 1947 and 1954.

It reveals that among factors which indicate a good prognosis are: (1) male sex, (2) age under 40 on admission, (3) duration of arthritis of less than a year before admission, (4) unilateral joint involvement at the onset.

This is without doubt the most important book about rheumatoid arthritis to appear for a long time.

**The Glaucomas.** By H. Saul Sugar, M.D., F.A.C.S. 2nd ed. (Pp. x + 516; illustrated. £5 5s. 0d.) London: Cassell & Co. New York: Paul B. Hoeber Inc. 1958.

The second edition of Sugar's monograph on glaucoma has made its appearance six years after the first. As would be expected it has increased in size because of the immense amount of work which has been carried out in the interim period. The highlights of advance include tonography as a method of examination and the information which it has yielded; the introduction of Diamox as a therapeutic agent; the reintroduction of peripheral iridectomy as standard surgery for early closed-angle glaucoma; the demonstration of aqueous veins and their pathways from Schlemm's canal and the biochemical discoveries from a close study of the intra-ocular fluid.

Although the new work has entailed a revision of the text it has not lost its unity. Each chapter deals with a circumscribed aspect and is complete in itself. The busy clinician need not be fearful of complicated technical jargon because all sides of the glaucoma

question are tackled with equal facility and are carefully and clearly described. With such a vast literature from which to choose, discretion has been exercised and the result is a pleasing and rounded discourse on a subject which is beginning to show signs of yielding at last to the ceaseless pressure of research.

**Clinical Heart Disease.** By Samuel A. Levine, M.D., F.A.C.P. 5th ed. (Pp. vi + 673; illustrated. 66s. 6d.) Philadelphia and London: W. B. Saunders & Co. 1958.

This well-known work, with its sustained clinical bedside methods, has now reached its fifth edition and covers the advances that have taken place in the past six years in the surgery of congenital and acquired heart disease. Further advances in electrocardiography and vectorcardiography are also discussed but the chief merit of this book lies in its practical nature. The important aspects of diagnosis, prognosis and treatment of heart disease at the bedside are emphasized and the book will be of value not only to the practising physician but also to the family doctor.

There is some repetition throughout, but this may be excused on the grounds that each chapter is meant to be self-contained. A noteworthy feature is the successful attempt to integrate clinical and laboratory studies for the practising clinician.

**Endocrine Aspects of Breast Cancer.** Proceedings of a Conference held at the University of Glasgow, 8th to 10th July 1957. Ed.: Alastair R. Currie, B.Sc., M.B., F.R.C.P.Ed. Foreword by C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.Ed., F.R.F.P.S. (Pp. xvi + 340; illustrated. 37s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

Everybody realizes the importance of the endocrine system in relation to breast cancer, and indeed to the whole cancer riddle.

The book is a report of the proceedings of a conference held in Glasgow during July 1957, and the editor, Dr. Alastair Currie, is to be congratulated on publishing it so promptly.

The report is divided into four parts, Clinical, Pathological, Study of Hormones, and Experimental Pathology.

There is an excellent discussion and summary at the end of each part, and a review of the conference seen as a whole by Prof. C. F. W. Illingworth.

This fascinating book is a necessity for every clinician who is treating cancer of the breast, as well as for every laboratory worker. Even if much of the work has been described previously in separate articles, this book brings the essence of the work together in a very readable volume.

**Clinical Neuro-ophthalmology.** By Frank B. Walsh, M.D., F.R.C.S.Ed., D.Sc. (W.A.-Hon.). 2nd ed. (Pp. xvi + 1294; illustrated. 231s.) London: Baillière, Tindall & Cox Ltd. 1957.

The new edition of this very fine book contains a comprehensive collection of all that pertains to neuro-ophthalmology.

Whether these vast and expensive books can continue to expand every few years is very doubtful. There is no evidence that the first edition has been pruned and several sections show signs of neglect. Thus neuroradiology of the posterior fossa is dismissed as being ineffective in diagnosis, yet the newest techniques now widely used are not mentioned. Whilst electroretinography may have only limited application in clinical problems, research in the subject continues, but this is not recognized and the original text is unaltered. A section is devoted to electroencephalography, an ancillary diagnostic aid which has contributed much during the past decade to this aspect of neurology. But again the text and its references are identical in the two editions and are now, of course, quite out of date. The dreadful EEG samples seen in 1947 appear again; they have only a historical value.

These are but small criticisms, however, of a work which now ranks as one of the more important reference books on the subject and one which can be strongly recommended.

**Current Therapy 1958.** Latest approved methods of treatment for the practicing physician. Ed.: Howard F. Conn, M.D. (Pp. xxx + 827. 84s.) Philadelphia and London: W. B. Saunders & Co. 1958.

Any book on therapeutics which includes details of the administration of chlorothiazide must appear to British eyes to be very much up to date. This, together with most advances one wishes to refer to, will be found in the latest edition of this well-known book. Its real practical value to both consultants and general practitioners is fully maintained, and it is reassuring to know that it is available for reference.

**Cancer.** Ed.: Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Vol. I. (Pp. x + 539 + 19; illustrated. 85s.) Vol. II. (Pp. ix + 641 + 25; illustrated. 85s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

These are the first two volumes of a projected multivolume work of reference covering all aspects of cancer. Volume I is entitled "Research into Causation", and Volume II "Pathology of Malignant Tumours". The contributors to Volume I are almost exactly balanced between Britain and America, eight being from Britain and six from America. The thirty contributors to the second volume are mostly from Britain, the minority consisting of three Americans, one Australian, and Doctor Pao-Chang Hou of Hong Kong. In the English-speaking world, the editor has thus, as befits his subject, been international in his choice of contributors.

The work starts with a brief historical review. One might object that it is unfair to blame Galen himself for overshadowing his successors; and to attribute the origin of the hormonal therapy of cancer to John Hunter is hagiology rather than history. It is fitting that the next two chapters are by the late Sir Ernest Kennaway, the first on the incubation period of cancer in man, and the second on the carcinogenic effect of cholesterol. Other chapters follow on carcinogenesis, cell chemistry, hormones, viruses, genetics, and nutrition. It is interesting to note the hints the different authors give of their views of the possible causation of cancer: Kennaway prefers "to suggest questions rather than answer them"; for Clark Griffith, "With an understanding of the mechanism of carcinogenesis it may be possible to block the sequence at one stage or another"; and for Huepper, "The circumstantial and factual information available concerning environmental carcinogenesis and cancer justifies the view that the prospect of their ultimate conquest by suitable preventative and therapeutic measures may be considered to be reasonably good". Bett, however, aptly sums up the present position in his article on the history of cancer: "The history of cancer chronicled thus far is the history of errors, of illusions, of disappointments, of occasional triumphs. The smile of the Sphinx continues inscrutable."

Volume II on pathology, being largely morbid anatomy and histology, lends itself more to factual analysis and classification. The names of many of the contributors are closely linked with their subject—Willis on the method of spread of malignant tumours, Dukes on the colon and rectum, Thackray on the salivary glands and Thomson on the thymus. The article by Symmers on malignant diseases of the lympho-reticular system is noteworthy for the account of the historical development and the definition of the terms used in this difficult subdivision of neoplasia.

It is interesting to compare the American and English systems of references used apparently at will by the different contributors. In the opinion of the reviewer, the American system, giving the full title of each reference, establishes itself as by far the more valuable.

In his preface, Mr. Ronald Raven, the editor, writes: "There is need for a close partnership of all who are engaged in different aspects of the work (on cancer) and the facilities for quick access to information concerning advances being made in fields other than their own." These volumes are a real contribution towards this laudable aim, and the editor is to be congratulated on the bevy of talent he has assembled.

**The Compleat Pediatrician.** By W. C. Davison, M.D., and Jeana Davison Levinthal, M.D. (Pp. vi + 257. 35s.) London: Staples Press Ltd. 1958.

This is a most useful book, which constant rewriting and expanding through seven editions[1] has rendered very fairly worthy of its ambitious title; it is obviously the product of immense experience and a great deal of team-work directed by a mature and balanced mind. In his introduction the author states that his idea is to avoid the old-fashioned type of pædiatric textbook. He has given us a vast but comprehensible mass of information and references.

The book shows no evidence of the "scissors and paste" method of compilation which fills so many books of the "synopsis" type with untested and inaccurate statements. Reading it will not make a pædiatrician, any more than studying Roget's "Thesaurus" (a book it resembles in many ways) will make a writer; but there are no workers in the field of which it treats who will not find stimulation and instruction in its study.

[1]7th edition in the U.S.A.; 1st edition in Great Britain.

# Section of Radiology

President—E. DUFF GRAY, M.A., M.D.

[*February* 21, 1958]

## Benign Lesions of the Pyloric Antrum Simulating Carcinoma [*Summary*]

By J. N. PATTINSON, M.B., F.F.R., and G. OSBORNE, M.D., M.R.C.P., D.M.R.D.
*The Middlesex Hospital, London*

DEFORMITIES of the pyloric antrum seen at the Middlesex Hospital during a period of five years were reviewed. 7 cases came to light in which a deformity thought to be due to an annular carcinoma was found to be benign. In 3 cases the appearance was due to fibrosis associated with a low lesser curve ulcer. In 2 there was pyloric hypertrophy with a duodenal ulcer in one case and a benign duodenal tumour in the other. In 1 patient, considered inoperable and re-examined a year later when the antrum appeared normal, the deformity was temporary and must have been due to spasm or œdema. In 1 the antrum was adherent to the gall-bladder and there was evidence of a healed prepyloric ulcer.

The problem of the concentrically narrowed antrum has been discussed often before. In some of the reported cases the antrum appeared normal at re-examination using an antispasmodic. In others, at laparotomy intermittent spasm of the antrum was seen or was provoked by manipulation. In most the abnormality was found to be due to fibrosis in or around the antrum or to pyloric hypertrophy with or without a peptic ulcer in the vicinity or at a higher level (Jenkinson and Latteier, 1943; Jenkinson and Hamernik, 1948; Cohn and Gold, 1948; Flood, 1950; Balint and Slater, 1954).

In our cases antral carcinoma was suspected because of the narrowing and absence of peristalsis. In each case, however, the edge was smooth, without "half-shadow" effect, "shouldering" or intraluminal filling defect, whereas in all the antral carcinomas seen during this period one or more of these signs were present.

On the other hand, rarely this type of deformity is due to carcinoma. (This point was illustrated by a case seen at St. Bartholomew's Hospital, shown by courtesy of Dr. R. A. Kemp Harper.) Nor is it safe to rely on a radiological diagnosis of pyloric hypertrophy. The indentation of the base of the cap claimed by Kirklin and Harris (1933) to be almost pathognomonic was seen in two of our antral carcinomas where the growth had invaded the duodenum. Also, the local ulceration with which pyloric hypertrophy is often associated (Desmond and Swynnerton, 1957) may be malignant (Albot and Magnier, 1953).

At laparotomy it is not always possible to decide if the lesion is benign or malignant. This was the position in 2 of the 6 cases submitted to operation.

It happens that gastroscopy was not performed in any of these cases, though this problem can sometimes be solved in this way.

It seems that this type of antral deformity may be due to carcinoma but is more likely to be due to a benign condition. The patient should be re-examined using an antispasmodic and if doubt remains gastroscopy should be performed. It is suggested that this type of deformity is not good enough evidence of malignancy to outweigh normal gastroscopy findings.

### REFERENCES

ALBOT, G., and MAGNIER, F. (1953) *Arch. Mal. Appar. dig.*, **42**, 347.
BALINT, J. A., and SLATER, J. D. H. (1954) *Gastroenterologia, Basel*, **82**, 330.
COHN, A. L., and GOLD, R. L. (1948) *Gastroenterology*, **10**, 782.
DESMOND, A. M., and SWYNNERTON, B. F. (1957) *Brit. med. J.*, i, 968.
FLOOD, C. A. (1950) *Gastroenterology*, **15**, 399.
JENKINSON, E. L., and HAMERNIK, F. J. (1948) *Radiology*, **6**, 798.
——, and LATTEIER, K. K. (1943) *Radiology*, **41**, 444.
KIRKLIN, B. R., and HARRIS, M. T. (1933) *Amer. J. Roentgenol.*, **29**, 437.

## The Radiological Diagnosis of Malignant Gastric Ulcer [*Summary*]

By B. GREEN, M.R.C.S., L.R.C.P., D.M.R.D., and R. A. KEMP HARPER, M.D.
*London*

A REVIEW of all the malignant gastric ulcers encountered over a period of eight years was carried out, and the radiological features assessed in comparison with the features generally reported as indicating the presence of malignancy.

It was found that many histories indicated long periods of gastric upset and agreed with the pathological interpretation that malignancy had supervened on a benign ulcer.

The following points were made:

(1) Ulcers may project beyond the gastric lumen, and an intra-luminal site is not essential to the diagnosis.

(2) Mucosal folds may run up to the edge of the crater and are not necessarily interrupted at some distance from the ulcer.

(3) Long irregular shallow ulcers are often malignant.

(4) A wide translucent band indicating a very thick edge to the ulcer is very often found in malignant ulcers.

(5) Angulation at the edge of the ulcer is a frequent sign in malignant ulcer.

(6) Malignant ulcers occur as frequently above the incisura as in the antrum or pyloric area.

(7) An ulcer which shows a fluid level within it when the patient is examined in the erect posture is almost invariably benign.

## Headache and Gastric Emptying Time

By L. S. Carstairs, M.B., B.S., D.M.R.

*Royal Northern Hospital, London*

Headache, particularly of the migrainous type, is often associated with a delay in gastric evacuation. My reason for presenting the subject is that it does not appear to be well recognized in my own age group. In a search of the current radiological textbooks I could not find a specific statement. The nearest reference was in "Roentgen-Diagnostics" (Schinz *et al.*, 1954) when, after a discussion of gastric emptying, it is said "The emptying of the stomach may be influenced on a purely psychogenic basis. It has been shown that in a patient with an otherwise normal stomach, pylorospasm with retention may occur under circumstances of anxiety and fear". However, Hurst *et al.* (1929) made the following clear-cut statement: "I have saved several patients from undergoing an operation for supposed pyloric obstruction when they were really suffering from migraine. If it is remembered that attacks of vomiting without abdominal pain are rarely due to abdominal disease, and that the association of headache with nausea and vomiting is most frequently due to migraine, such mistakes would never be made. The confusion is sometimes increased by the fact that an X-ray examination has been carried out during an attack of migraine, and as this completely inhibits gastric activity, prolonged stasis may occur. I have seen several reports from experienced radiologists in which pyloric obstruction was diagnosed because of stasis of this kind, a subsequent examination in a period of freedom showing that evacuation took place without delay. There is little excuse for such mistakes, as pyloric obstruction is accompanied by peristalsis of exceptional vigour, whereas during an attack of migraine, peristalsis is more or less in abeyance." This statement was repeated by Arafa (1933) in his textbook of gastro-enterology, and in 1936 there was a report by Kaufman and Levine of a patient who had acute gastric dilatation during a prolonged attack of migraine. A subsequent examination showed a normal stomach with normal emptying.

For my own part I was told of this association by the late Dr. G. R. Mather Cordiner many years ago. At a conservative estimate I would say that 30 examples of major delay have been encountered, that is patients without discoverable pathology in the upper alimentary tract who, two hours after taking the barium, have had large gastric residues with poor transit through the small gut and who have been suffering from severe headache, often migrainous in character, but not always so, throughout. This does not include those patients whose impending faint is heralded by a sudden loss of gastric tone and peristalsis. I might also add an impression which I know is shared by others that delayed contraction of the gall-bladder after a fatty meal is sometimes accompanied by a headache.

The observation regarding this association can be divided in two parts. *First:* During the initial screening there is pyloroduodenal hypertonia, the tone of the stomach is moderately good but peristalsis is poor. Subsequently, the general tone appears to be less good and the stomach becomes relatively atonic. It is not dilated. This state of affairs can be produced by pyloric or duodenal obstruction, antral ulceration and ulceration close to the incisura angularis. The examination may reveal no lesion and, if the patient is then questioned, the fact that he has a headache may be disclosed. Further questioning may point to a relationship between his current abdominal symptoms and migraine. *Second:* All barium meal patients have a routine two-hour film which is examined by the radiologist before the patient is allowed to leave. In the case of a patient whose initial examination was normal but who has a large two-hour residue, it is always worth while asking if he has a headache. Often the fact is self-evident, the patient being thoroughly

unhappy and in obvious distress. Attempts are then made to cut short the attack as it is unjustifiable to keep the patient in this condition merely to see for how long his stomach will retain the barium. Naturally, we know of no certain method of terminating a migraine. (Five examples of this condition were then demonstrated, together with one case as a reminder that ulceration and migraine can co-exist.)

The physiology of migraine, headache, nausea and vomiting is complex and not fully known. The mass of experimental and observational evidence relating to the control of gastric activities has been summarized by Alvarez (1948). There is a very full summary of all the clinical aspects of migraine in the monograph by Henry Riley (1932), while the physiology of headache in all its forms has been excellently surveyed by Moench (1951).

The problem of delayed gastric evacuation associated with headache has not, so far as I can find, been investigated as a single entity although many researches bear directly on one or other of its aspects. A few selected observations follow:

(*a*) The migraine stomach most closely resembles the stomach following vagotomy.

(*b*) The acts of retching and vomiting do not necessarily depend on distension of any portion of the alimentary tract, although they can be induced by such distension or the instillation of noxious substances.

(*c*) Nausea is a subjective sensation which can be initiated through many pathways, central and peripheral. The problem arises as to whether sensations of nausea, in the average subject, as opposed to the experimental animal, are mediated through a phase of gastric hypotonia. In migraine, nausea with or without vomiting is almost a constant feature. The initiating factor in migraine may not be discoverable and Alvarez regards the condition more as a hereditary mental disease than one produced by organic disorders of the body. Suggestions made to explain the abdominal symptoms of migraine have almost all been directed to explaining the vomiting. Very few suggestions have been made regarding the preceding gastric hypotonia since this does not appear to have been generally recognized.

(*d*) The work of Stewart Wolf (1943) is apposite to this problem. He carried out a series of experiments on himself and volunteers and subsequently, with H. G. Wolff (1947), on Tom, the man with a gastric fistula who formed the subject of their book "The Human Gastric Function". These experiments were repeated many times and the results were always comparable. On syringing one external auditory meatus with cold water up to the stage of nystagmus, there was an interval during which the subject either had no abnormal sensations or developed nausea. Irrespective of whether or not nausea was experienced, there was a prompt cessation of gastric motility. If nausea was experienced then, in addition, there was a reduction in gastric acidity with an increased production of mucus. If Prostigmin and atropine were given beforehand, so that gastric motility was enhanced, the procedure had no effect on gastric motility and no feeling of nausea developed. He concluded that, in his experiments, nausea could only be induced if there was a pre-existing gastric hypomotility. He was not able to define further the connexion between the stimulus and the subjective sensation.

(*e*) Delayed gastric evacuation with headache is not always associated with nausea and there do appear to be patients in whom the abdominal symptoms of migraine can occur without headache.

To sum up, it is important for the radiologist to know of this syndrome so that, when faced with the condition outlined earlier, he will be able to offer an explanation and will be deterred from making an error in diagnosis. It must not be forgotten that patients may suffer from both migraine and peptic ulceration.

## REFERENCES


ALVAREZ, W. C. (1948) Introduction to Gastro-Enterology, 4th edit. London.

ARAFA, M. A. (1933) Gastro-Enterology. London; p. 132.

CORDINER, G. R. M. (1942) Personal communication.

HURST, A. F., *et al.* (1929) Gastric and Duodenal Ulcer. London; p. 233.

KAUFMAN, S., and LEVINE, I. (1936) *Radiology*, **27**, 301.

MOENCH, L. (1951) Headache. Chicago.

RILEY, H. A. (1932) *Bull. neurol. Inst., N.Y.*, **2**, 429.

SCHINZ, H. R., *et al.*, (1954) Roentgen-Diagnostics. London; **4**, 3243.

WOLF, S. (1943) *J. clin. Invest.*, **22**, 877.

——, and WOLFF, H. G. (1947) Human Gastric Function. London.


## DISCUSSION

**Mr. Norman C. Tanner:** For about twenty years I have been connected with a gastroscopic clinic, where on one day a week we gastroscope patients from other hospitals most of whom are sent because the radiological evidence is either negative or inconclusive. In this part of our work I think the examination gives particular help in two classes of case: (1) the patient who has bled and has negative radiographic findings, and (2) the patient with a radiological lesion which may or may not be a cancer.

Of the latter type of case there is no doubt that with its aid one can, not infrequently, confidently exclude malignancy and the finding most commonly made is that the filling defect is in reality an encircling fibrosis or less often spasm, associated with a small posterior wall or lesser curve healed or healing ulcer. On the contrary occasionally an hour-glass stomach turns out on gastroscopy to be an infiltrative cancer.

The most anxious and difficult decisions concern doubtful radiological abnormalities of the pyloric antrum.

If an ulcer is present at the angulus a successful gastroscopy should give good views of the ulcer and this together with confirmation of mobility of the antrum might enable a diagnosis of innocence to be made.

We have confirmed the innocence of ulcers on the greater curve side of the distal antrum on occasions, but the lesser curve side of the distal antrum is a much more difficult proposition. With patience one may find the antral peristaltic waves become strong enough to view the ulcer or scar, but the view may be either transitory or tangential. In a significant proportion of ulcers of the distal lesser curve, the extra-gastric adhesions will hold this part up and no view of the lesser curve beyond the angulus may be obtained. Under such circumstances even a deep ulcer cancer may be missed.

On the other hand some helpful evidence may be obtained. In nearly all cases the mobility of the greater curve may be assessed and a smoothly undulating mucosa in this region will at least exclude an encircling carcinoma. Furthermore if there is an encircling carcinoma the appearances of the part in view are striking to the experienced gastroscopist by the local and unusual stillness, asymmetry, colour changes, superficial mucosal irregularities, erosions and so forth.

One of the most important things in gastroscopy is to know what parts of the stomach one has or has not seen. With patience and the avoidance of too much inflation the antrum and pylorus can be seen in most cases. A circular ring of spasm is not the pylorus. I have even seen an antral wave run smoothly to finish at a small final contraction and yet there was a localized carcinoma in the pyloric ring. The pylorus has only been seen when, not only does the wave contract to a small opening, but also the mucosa inside the opening evenly prolapses back into the stomach—demonstrating the laxity of the intrapyloric mucosa.

Gastroscopy is of help in differentiating simple from malignant ulcers. Many ulcers which appear innocent at radiography have obvious malignant appearances on gastroscopy. There is, of course, a small residuum of cancers which look innocent on gastroscopy or even after resection. To eliminate this group I am sure the safest course is to repeat the gastroscopy after two to three weeks' *bed rest* and regular meals. If it does not show definite signs of healing then it should be treated as malign. I have never known an ulcer to be seen to heal gastroscopically and later turn out to be malignant.

**Dr. G. Steiner:** The interesting cases referred to by Dr. Pattinson are mostly examples of a definite radiological entity, described as "ligneous gastritis", "chronic infiltrative gastritis" or "stenosing gastritis". In the majority, but not invariably, they are secondary to a peptic prepyloric ulcer and are characterized on section by infiltration with leucocytes and lymphocytes often of the whole thickness of the gastric wall, with or without hypertrophy of the muscle layer.



FIG. 1.—Widespread ligneous infiltration including the muscular layer, around an irregular prepyloric peptic ulcer.

Dr. Pattinson's slides showed the appearances with the lumen filled to capacity. We have, for over thirty years, studied the mucosal pattern using a thin coating with barium in attempts to assess how deeply lesions have extended within the thickness of the wall and to further the differential diagnosis of early carcinoma. Study of the mucosal relief similar in manner to that classically described by Berg (1931) permitted us to define lesions confined to the mucosa, others involving at least the submucosa and infiltrations into the muscular layer. Also lesions arising in the muscularis and such confined to the peritoneal coat. These relief studies depict the pathological anatomy as revealed after operation often very closely and histology has in many instances confirmed not only the differentiation from malignancy, but also the radiological assessment of the strata involved.

The following slides were demonstrated: (1) Predominantly submucosal extension with radial conversion of rugæ. (2) Widespread "ligneous" infiltration including the muscularis propria around an irregular prepyloric peptic ulcer (Fig. 1). (3) Extensive rigid infiltration with concentrical stenosis which the surgeon at operation considered to be neoplastic. Histology proved radiology to




FIG. 2.—Very small circumscribed fibrosis of greater curve, secondary to healing juxtapyloric ulcer. Normal evacuation. Similar to but still smaller than case of Fig. 3 in Steiner (1949).



FIG. 3.—Widespread polyposis, normal calibre and sharp definition of intervening mucosal folds.

be correct. (4) A late result, consisting of a sharply outlined small area of thickening near a healing peptic ulcer. Histology: "Chronic circumscribed fibrous induration secondary to peptic ulcer" (Fig. 2). (5) The warty type of idiopathic gastritis is contrasted with multiple polyposis (Fig. 3) and a disseminated polypoid type of carcinoma. (6) One of several instances of correctly diagnosed perivisceritic stenosis without intrinsic lesion, at operation shown to be due to a band of adhesion. After this was cut the prepyloric portion unfolded completely, the pylorus was patent and no thickening of the gastric wall was felt.

## REFERENCES

BERG, H. H. (1931) Röntgenuntersuchungen am Innenrelief des Verdauungskanals. 2nd edit. Leipzig.
STEINER, G. (1933) *Med. Klinik*, **29**, 1484.
—— (1938) *Röntgenpraxis*, **10**, 507.
—— (1949) *Brit. J. Radiol.*, **22**, 25.
—— (1950) Sixth *Int. Congr. Radiol.*, London, p. 85 (abstract).

[*April* 18, 1958]

# Some Radiological Aspects of Biliary Tract Disease [*Abridged*]

## PRESIDENT'S ADDRESS

By E. DUFF GRAY, M.A., M.D.
*Manchester*

### *Radiological Methods*

SINCE the original work on excretion cholecystography by Graham and Cole (1924), several important developments in the radiological examination of the biliary tract have taken place.

Pheniodol was introduced in 1940 as an improved oral contrast medium, largely because of its less unpleasant side-effects than those of the earlier media and because of its greater freedom from confusing shadows due to bowel residue. In 1951, iopanoic acid (or Telepaque), a medium containing much more iodine than pheniodol, began to be widely adopted for routine use. In recent years, Biligrafin, an intravenous excretion medium, first introduced by Frommhold (1953), has been employed with increasing frequency. This medium not only allows demonstration of the gall-bladder but also of the major bile ducts in most cases. Its particular advantage is that the major bile ducts can usually be outlined even in a patient whose gall-bladder has been removed.

Among easily accessible articles on the use of these media are those by Kemp (1943), Stevenson (1952), Gordon (1953), Sutton and Tillett (1954), Aldridge (1955) and Don and Campbell (1956).

Coincident with the development of contrast media with different qualities, which will be referred to later, there has been a striking development of radiological methods generally so that nowadays we have the advantages of many accessory techniques which serve to improve the value of the radiological investigation of the biliary system. As examples of these newer methods may be mentioned the following: Multiple localized films under screen observation, permitting minor variations in applied pressure over the gall-bladder; postural alterations of the patient to displace intestinal gas and to show "levels"; tomography, especially to demonstrate the common bile duct; and, most recently, the use of the image amplifier with ciné recording. Various combined techniques have also been suggested (Aldridge, 1955; Mitchell, 1956; Johnstone and Sumerling, 1957).

### *Anatomical and Physiological Considerations*

The pressure system in the biliary tract consists of three main elements: the secretory pressure in the liver, the resistance to free emptying of the common bile duct by a muscular mechanism at its lower end and the combination of muscular tone and contractile power of the gall-bladder. The first of these pressures is believed to remain constant but the second and third vary according to requirements and are of special interest to radiologists.

#### *The Distal Common Bile Duct*

Since Oddi's first description of a sphincter at the lower end of the common bile duct, much argument has taken place as to its precise anatomical structure. Agreement even now has not been reached but Boyden (1957) has published some superb anatomical studies which seem to make it certain that there is an intrinsic sphincter in this region quite distinct from the duodenal musculature. It is evidently a complex structure which includes not only muscle fibres surrounding the duct itself but additional fibres derived from the circular muscle of the duodenum, anchoring the duct to the duodenum and compressing it against the wall. There are also muscle fibres around the major duodenal papilla compressing the outlets of both the common duct and the pancreatic duct.

[A short ciné film was now shown. This film, entitled "The common bile duct: a demonstration of peristalsis in certain animals and man", was made by Mr. William Burnett in the Department of Surgery, Glasgow University. It illustrates the anatomical variations of the biliary tract in several species of animals and ends with a demonstration of the radiological appearances of the common bile duct at post-operative cholangiography, using the image amplifier with ciné attachment.]

Burnett (1958) is of the opinion that muscular contraction takes place over a considerable extent of the common bile duct and not only at its distal part where the sphincter is situated.

#### *The Common Bile Duct in Relation to the Pancreatic Duct*

Considerable anatomical variation is known to exist in the relation of the common bile duct to the main pancreatic duct. The two ducts may enter the second part of the duodenum separately but, much more commonly, they join at a variable distance proximal to the papilla. According to Hjorth (1947), who studied this matter by post-mortem injection into the tail of the pancreas, such a confluence of the ducts occurs in 86% of cases. Other observers give lesser percentages, between 60% and 75% being more usual figures.

The importance of the question of reflux from one duct into the other lies in the possibility of pancreatic secretion entering the biliary tract and bile entering the pancreas. It is believed that reflux in either direction may be of ætiological significance in cholecystitis and pancreatitis respectively and it is on this theory that the operation of sphincterotomy has largely been developed.

Reflux of bile into the pancreatic duct has never been demonstrated by excretion cholecystangiography but it is a frequent occurrence in direct cholangiography. In my experience, the distal part of the pancreatic duct is visualized in about 25% of cases in cholangiography through a "T" tube after cholecystectomy. This is not nearly as high a figure as one might expect from the anatomical frequency of confluence of the two ducts but, of course, reflux must depend not only on the anatomical conditions but also on the relative pressures in the ducts and in their confluent channel at the time of injection.

#### *Contraction of the Gall-bladder*

Soon after the introduction of excretion cholecystography by Graham and Cole, the anatomist Boyden (1928) demonstrated radiographically the contraction of the gall-bladder which takes place in response to the ingestion of egg yolk and cream. Boyden showed, in a series of normal subjects, that contraction commenced within two minutes of the meal. This was followed by a short pause and then contraction went on steadily and fairly rapidly up to about thirty minutes and later more slowly to reach a maximum in between one and two hours. Females, in general, showed a more rapid emptying but there was a wide

variation in emptying time—between thirty minutes and four and a half hours. The time was found by re-examination to remain constant for the individual.

The mechanism of gall-bladder contraction is believed to be a direct hormonal effect due to the elaboration of cholecystokinin by the duodenal mucosa in response to the stimulus of food, particularly egg yolk and fat, entering the second part. (Various preparations of vegetable fat are quite satisfactory in this respect.)

Recently, pure cholecystokinin has been prepared in crystalline form and has been used as an intravenous injection to produce contraction of the gall-bladder (Adlercreutz *et al.*, 1957; Brodén, 1958).

The type of contraction seen after cholecystokinin injection is different from that following a fat-containing meal—there is a much more rapid contraction, reaching a maximum within twenty or thirty minutes. This is followed by a relaxation of the gall-bladder which returns to its original size, though not, of course, to its original density, within the ensuing half-hour.

Although the examination can be conducted more rapidly and perhaps more scientifically, intravenous cholecystokinin is not likely to replace the original fat-meal method as a routine measure in radiological diagnosis because of several drawbacks, chief of which are: the potential danger of sensitization, the necessity of an intravenous injection and the added expense.

In my opinion, there is at present no certainty that a critical, volumetric analysis of gall-bladder emptying is worth the effort and expense involved. I believe that the value of examining gall-bladder contraction depends on (1) the improved chance of demonstrating small non-opaque stones and (2) the demonstration of the extra-hepatic ducts by the rapid discharge of contrast-laden bile from the gall-bladder.

*Qualities of the Contrast Media in Current Use*

It is important to appreciate that the three main types of contrast medium in current use (pheniodol, Telepaque, Biligrafin) have different qualities. All three media can outline the gall-bladder provided the cystic duct is patent but the conclusions to be drawn are not the same in each case.

With Biligrafin, this outlining is not dependent on an actively concentrating gall-bladder mucosa for the contrast medium enters the gall-bladder already sufficiently radiopaque for demonstration.

With pheniodol, the iodine-laden bile entering the gall-bladder is not radiopaque and becomes so only by the active withdrawal of water, which raises the iodine content of the concentrating bile. Therefore a demonstration of a gall-bladder shadow by pheniodol can be taken as proof that the mucosa is functioning.

Telepaque seems to occupy an intermediate position. A gall-bladder seen after Telepaque does not necessarily mean that much concentration has taken place. I believe that liver bile after Telepaque requires very little concentration in the gall-bladder to become radiopaque, and consequently Telepaque is not as good a test of gall-bladder function as pheniodol.

Support is given to this view by three observed facts: (1) The gall-bladder outlines densely much sooner after Telepaque than after pheniodol. (2) The common bile duct is occasionally demonstrable in cases where the gall-bladder has not outlined. (3) The hepatic and common bile ducts can be shown by Telepaque even in a patient whose gall-bladder has been removed and where there is therefore no question of bile concentration. Twiss *et al.* (1955) have used Telepaque in these circumstances with considerable success.

It has been recognized from the early days of cholecystography that a visualized gall-bladder does not necessarily mean that its mucosa is normal, whereas a gall-bladder that does not outline means, almost always, that a pathological process is present, either a blockage of the cystic duct or a grossly diseased mucosa, that is to say that the test is more likely to be unreliable when the gall-bladder is visualized than when it is not. Why therefore add to this possibility of error by using a medium such as Telepaque, which requires very little concentration?

It seems to me that the routine use of Telepaque results in many more gall-bladders being assumed to be normal when they are not.

Broadly speaking, the radiologist is concerned with three aspects of biliary tract disease—function of the gall-bladder, presence of gall stones, morphology of the tract. No single method of X-ray examination will often provide the best available answers under each of these headings.

For function, I believe *pheniodol* is the best medium. For the demonstration of non-opaque stones, *Telepaque* is the best and the most convenient. For anatomy, *Biligrafin*. All three may be necessary in a particular case but I like to start with pheniodol unless the plain film or the history gives a lead to the problem or it is known with certainty that the gall-bladder has been removed.

*The Routine X-ray Examination of the Biliary Tract*

With these considerations in mind, I have adopted the following basic plan as a routine in my department. At the patient's first visit a plain film of the whole abdomen is taken. This film is seen wet and the patient is interviewed by a radiologist, who arranges the next step—this will vary according to the findings of the plain film and the information derived from the patient and the clinical notes.

If the plain film gives certain evidence of gall-stones, oral cholecystography is unnecessary. If there are shadows possibly, but not certainly, due to gall-stones, cholecystography using Telepaque is arranged in order to resolve the doubt.

If the plain film shows no significant abnormality, arrangements are made for pheniodol cholecystography. At this second attendance, if there is a good gall-bladder outline on the standard "erect" and "prone" films, further films are taken after a fatty meal. (These films are omitted if there is positive evidence of non-opaque stones.) If, however, no shadow or a poor shadow is seen after pheniodol, arrangements are made for Telepaque cholecystography on the following day in order to improve the chances of showing non-opaque stones.

Biligrafin is held in reserve for those cases which still remain in doubt. I do not feel inclined to employ it without the approval of the referring clinician.

In those cases where cholecystectomy has been finally decided on, I like to offer to carry out a Biligrafin intravenous cholecystangiography and also a barium meal, if this has not already been done.

*The X-ray Examination of Jaundiced Patients*

No reliable and safe method of demonstrating the biliary tract in jaundice has so far been evolved. Biligrafin is perhaps worth trying if the serum bilirubin is under about 4 mg. or if the jaundice is very recent or is waning. Usually, however, the results will be disappointing. Aldridge (1955) has reported better results in jaundice than most observers. His technique includes the use of pethidine to produce spasm of the sphincter of Oddi.

Transhepatic cholangiography, a method of examination in which a needle is pushed blindly into the liver until it enters a dilated duct, has been recommended by several observers, including Mandl (1956) who obtained diagnostic films in about half his cases. In this country, however, the general view seems to be that the procedure does not justify its potential dangers.

The address concluded with the demonstrations of a number of slides and the discussion of examples of cases of special interest including the following: pancreatic calculi, gas in the biliary system, milk of calcium bile, cholecystitis glandularis proliferans cystica (diverticulosis of the gall-bladder), fixed mural translucencies due to papillomata and to localized cholesterolosis, enlargement of the gall-bladder after gastric operations and the cystic duct remnant in patients with a recurrence of symptoms after cholecystectomy.

## REFERENCES


ADLERCREUTZ, E., JORPES, E., MUTT, V., and WEGELIUS, C. (1957) *Arch. Mal. Appar. dig.*, **46,** 414.
ALDRIDGE, N. H. (1955) *J. Fac. Radiol.*, **6,** 243.
BOYDEN, E. A. (1928) *Anat. Rec.*, **40,** 147.
—— (1957) *Surg. Gynec. Obstet.*, **104,** 641.
BRODÉN, B. (1958) *Acta radiol., Stockh.*, **49,** 25.
BURNETT, W. (1958) Personal communication.
DON, C., and CAMPBELL, H. (1956) *J. Fac. Radiol.*, **7,** 149.
FROMMHOLD, W. (1953) *Fortschr. Röntgenstr.*, **79,** 283.
GORDON, I. R. S. (1953) *Quart. J. Med.*, **22,** 261.
GRAHAM, E. A., and COLE, W. H. (1924) *J. Amer. med. Ass.*, **82,** 613.
——, —— (1925) *Amer. J. Roentgenol.*, **14,** 48.
HJORTH, E. (1947) *Acta chir. scand.*, Suppl. 134.
JOHNSTONE, A. S., and SUMERLING, M. D. (1957) *Lancet*, ii, 1089.
KEMP, F. H. (1943) *Brit. med. J.*, ii, 674.
MANDL, F. (1956) *Chirurg*, **27,** 341 (quoted in 1957/58. Year Book of Radiology. Chicago; p. 228).
MITCHELL, D. J. (1956) *Brit. J. Radiol.*, **29,** 133.
STEVENSON, J. J. (1952) *Brit. J. Radiol.*, **25,** 531.
SUTTON, D., and TILLETT, J. V. (1954) *Brit. J. Radiol.*, **27,** 575.
TWISS, J. R., GILLETTE, L., BERENBAUM, S. L., POPPELL, M. H., and HANSSEN, E. C. (1955) *Arch. intern. Med.*, **95,** 59.

# Section of Medicine

President—W. A. BOURNE, M.A., M.D., F.R.C.P.

[*May* 20, 1958]

## DISCUSSION ON CLINICAL AND LABORATORY ASSESSMENT OF WATER AND ELECTROLYTE DISTURBANCES

**Dr. D. A. K. Black** (University of Manchester):

The attempt to define the part played by blood electrolytes in the symptoms of disease is beset by a number of difficulties, of which perhaps the most fundamental is the difficulty of distinguishing a simple association from a true causal relation. As flame photometry provides us with sodium and potassium concentrations in the serum of larger numbers of patients, the symptoms associated with high or low serum concentrations of these electrolytes increase in number, but not necessarily in significance. This difficulty might be met in theory by correcting the biochemical abnormality and observing the disappearance of symptoms; but the attempt to do this brings us up against the second difficulty, that the electrolyte present in serum, and thus readily available from sampling, is in dynamic equilibrium with a much larger amount of the same electrolyte in cells or in extracellular fluid. It is therefore virtually impossible to change serum concentrations without modifying either the cellular content of electrolyte or the distribution of body-fluid. The relative amounts of some electrolytes in the plasma compartment and in the whole body are set out in Table I.

TABLE I

| | Amount (mEq.) in: | | | |
|---|---|---|---|---|
| Electrolyte | Plasma | Extracellular fluid | Bone | Body (70 kg.) |
| Sodium | 420 | 1,260 | 1,500 | 3,500 |
| Potassium | 15 | 45 | 250 | 4,000 |
| Magnesium | 6 | 18 | 920 | 1,750 |
| Calcium | 15 | 45 | 57,500 | 58,000 |

*Note.*—A plasma volume of 3 litres and extracellular fluid volume of 9 litres are assumed. Estimated from various sources, including Shohl (1939). Non-ionic Ca and Mg are included.

The accessibility of extravascular electrolyte naturally varies, and electrolyte in bone is likely to be less rapidly mobilized than that in extracellular fluid. For potassium, which is mainly an intracellular electrolyte, it has been shown by the use of $^{42}K$ that exchange across the capillary wall is so rapid that over 90% of the potassium entering the kidney in the plasma is exchanged during one renal transit (Black *et al.*, 1956). These considerations make it seem likely that any abnormality in a serum electrolyte is attended by a corresponding or even greater alteration in the extravascular moiety of that electrolyte, which may be the real cause of any given symptom. Moreover, an abnormal serum electrolyte pattern is often associated with shifts of body-water and alterations of acid-base balance which cannot be left out of account in relation to symptoms.

While these difficulties no doubt demand a critical approach to suggested relations between serum electrolytes and symptoms, they do not compel us to deny that such relations exist, nor do they obliterate the value of estimation of the serum electrolytes, when the results are considered in relation to the whole clinical picture. The recognition of syndromes is of value in directing investigation towards the serum electrolyte pattern, and through that to the underlying disturbances of electrolyte metabolism. The clinical changes associated with hypernatræmia and hyponatræmia are much less definite than the changes which may accompany hyperkalæmia and hypokalæmia. This may well be because changes in serum concentration of sodium are much less specifically tied to sodium metabolism than are the corresponding changes in potassium: serum sodium concentration is directly affected by hydration, serum potassium only indirectly.

*Sodium.*—The sodium of plasma is in effective continuity with the sodium of extracellular fluid, and about half the sodium in the body is extracellular. The concentration of sodium in plasma is altered by change in the amount of water in the body, as well as by change in the amount of sodium. The serum sodium may be low both in patients who are clinically dehydrated and in patients who are œdematous; the common factor in these superficially diverse situations is an excess of water in the body relative to sodium and its accompanying anions. On the other hand, the serum sodium can be raised by giving hypertonic saline, or by restricting the intake of water. Partly because of this variety of clinical states which may be associated with the same concentration of serum sodium, the present tendency is to look on serum sodium as an indicator of the osmotic pressure of body-fluid rather than

as a direct determinant of any special group of symptoms—a viewpoint summarized in the catch phrase "osmotic stuffing". The general validity of the view that sodium concentration reflects osmolarity of body-fluid rather than the state of sodium balance *per se* has recently been strengthened by the careful studies of Wynn and Houghton (1957). They found that observed changes in serum sodium agreed very closely with those predicted from the change in water balance, and in the balances of sodium and potassium. The need to include change in potassium balance in order to predict change in serum sodium seems to me to show quite clearly that it is total osmotic balance, and not only sodium balance which determines sodium concentration in the body. From a clinical survey, Mason and Dryer (1957) have come to the same conclusion, that change in serum sodium level can be accounted for by external balance of water and electrolytes, and that internal shifts of sodium are of doubtful importance.

The symptoms ascribed to *hyponatræmia* are probably due to lowered osmolarity of body-fluid, and are seen in their least complicated form in water intoxication, as described clinically by Rowntree (1922) and Wynn and Rob (1954). Hyponatræmia is also seen in sodium depletion, and in patients with œdema who have been treated with a low-salt diet and diuretics. The symptoms include mental disturbances, at first apathy and disorientation, later convulsions and coma; variable alterations in the state of voluntary muscle, sometimes hypotonia and areflexia, in other patients cramp; and indications of smooth muscle disturbances, such as nausea and vomiting. The state of the circulation is variable, depending on associated hydration rather than on the serum sodium level. This is a confusing picture, but all the manifestations which I have mentioned have been reversed on occasion by hypertonic saline infusion, and I think they can be caused sometimes by hypo-osmolarity, although each of them has many other possible causes.

The symptoms associated with *hypernatræmia* are perhaps even more difficult to assess, because the most common cause of hypernatræmia is defective intake of water in a patient who is already apathetic or comatose. In hypernatræmia due to primary aldosteronism (Conn, 1955), or to infusion of hypertonic saline, thirst is outstanding. This is also true of hypernatræmia of voluntary water depletion, but clinical water depletion is often caused by failure of the thirst mechanism, so that thirst may be absent, or at least unexpressed. Severe water depletion is associated with serious mental disturbance, of which hyperosmolarity is a likely cause; in lifeboats, suicide has been observed after the drinking of sea-water.

*Potassium.*—Although the potassium of serum is so small both in concentration and in total amount relative to the potassium of cells, the evidence for ascribing specific symptoms to change in serum concentration of potassium is much stronger than the corresponding evidence for sodium. Experimentally, the demonstration of the critical effect of potassium concentration in the fluid perfusing the heart goes back to the classical studies of Ringer in 1883; and similar effects have been observed in both smooth and striated muscle. Familial periodic paralysis has long been accepted as a clinical analogue, although periodic paralysis is not always associated with hypokalæmia, and the importance of intracellular entry of sodium has recently been stressed (Conn *et al.*, 1957). Reversible muscle weakness has often been observed in states of potassium depletion, but the correlation with serum potassium concentration is not exact, being modified by the calcium concentration, the pH of serum, and no doubt other factors as well. A specific study of hypokalæmia has been made by Surawicz *et al.* (1957) who gave amounts of potassium sufficient to raise the serum level, but not to correct materially the intracellular deficit of potassium; the situation is less clear with hyperkalæmia, which does not lend itself to leisurely observation before treatment is given.

The most readily demonstrable effects of *hypokalæmia* are those on skeletal and on cardiac muscle. Weakness, hypotonia and loss of reflexes represent an effect predictable from the experimental observations. Tetany has also been observed, however, sometimes during treatment and associated with hypocalcæmia; but also with normal levels of serum calcium. Fourman (1954) concludes that this second form of tetany associated with potassium depletion cannot be accounted for by changes in extracellular fluid, but is possibly related to increase in intracellular sodium. The cardiac abnormalities associated with hypokalæmia include tachycardia and arrhythmia, and ECG changes such as flattening or inversion of the T wave and the appearance of a U wave. Increased susceptibility to the action of digitalis, therapeutic or toxic, is an important correlate of hypokalæmia. Although mental disturbances and paralytic ileus are often regarded as manifestations of intracellular potassium deficit, they have been seen to disappear, along with hypokalæmia, when only small amounts of potassium have been given (Surawicz *et al.*, 1957). More definitely associated with intracellular potassium depletion are those symptoms which have a definite counterpart in morbid anatomy, such as polyuria and thirst associated with vacuolar nephropathy, and cardiac failure associated with myocardial necrosis.

*Hyperkalæmia* also has notable effects on cardiac and on skeletal muscle. With toxic levels of serum potassium, the heart action becomes irregular, and this may go on to arrest

in diastole, preceded by a period of idioventricular rhythm or of ventricular fibrillation. In addition, there is peaking of the T-wave, and later gross distortion of the QRS complex. Paræsthesiæ can be induced even in normal people by large doses of oral potassium. A few patients with hyperkalæmia have had paralysis, which may be widespread and ascending, with diaphragmatic involvement.

*Magnesium.*—Reliable estimations of the concentration of magnesium in plasma are much less generally available than accurate sodium and potassium concentrations. The clinical picture of magnesium depletion and excess is still ill-defined, quite apart from its analysis into effects of serum-concentration changes and effects of intracellular depletion. Excess of magnesium, which may occur in uræmic patients given magnesium salts, has caused drowsiness and coma. Riedesel and Folk (1954) have made the intriguing observation that the serum magnesium is increased in hibernating bats. Wacker and Vallee (1957) have found that the serum magnesium was commonly raised in patients with renal failure, and could be lowered by dialysis, with apparent relief of drowsiness and muscle weakness, and reversion towards normal of an ECG pattern similar to that of hyperkalæmia, but not associated with a serum potassium high enough to account for the changes.

Moderate depletion of magnesium has been induced experimentally in man, with no very definite clinical effects (Fitzgerald and Fourman, 1956). More extensive depletions have arisen in patients losing fluid, with replacement over long periods by solutions not containing magnesium. The reported symptoms include muscle twitching and tremor, agitation and delirium, and convulsions leading to coma (Flink *et al.*, 1957). Card (1958) has observed a patient with massive loss of fluid from an ileostomy who had an episode of clear-cut agitation which responded critically to the infusion of magnesium; this patient showed no tremor, tetany or increase in reflexes.

REFERENCES


Black, D. A. K., Davies, H. E. F., Emery, E. W., and Wade, E. G. (1956) *Clin. Sci.*, **15**, 277.
Card, W. I. (1958) Communication to Ciba Colloquium on "Water and electrolyte metabolism in relation to age and sex". London; p. 301.
Conn, J. W. (1955) *J. Lab. clin. Med.*, **45**, 661.
——, Louis, L. H., Fajans, S. S., Streeten, D. H., and Johnson, R. D. (1957) *Lancet*, i, 802.
Fitzgerald, M. G., and Fourman, P. (1956) *Clin. Sci.*, **15**, 635.
Flink, E. B., *et al.* (1957) *Ann. intern. Med.*, **47**, 956.
Fourman, P. (1954) *Lancet*, ii, 525.
Mason, E. R., and Dryer, R. L. (1957) *Surg. Gynec. Obstet.*, **105**, 273.
Riedesel, M. L., and Folk, G. E. (1954) *Amer. J. Physiol.*, **179**, 665.
Ringer, S. (1883) *J. Physiol.*, **4**, 29.
Rowntree, L. G. (1922) *Physiol. Rev.*, **2**, 116.
Shohl, A. T. (1939) Mineral Metabolism. New York.
Surawicz, B., *et al.* (1957) *Amer. J. med. Sci.*, **233**, 603.
Wacker, W. E. C., and Vallee, B. L. (1957) *New Engl. J. Med.*, **257**, 1254.
Wynn, V., and Houghton, B. J. (1957) *Quart. J. Med.*, **26**, 375.
——, and Rob, C. G. (1954) *Lancet*, i, 587.


**Professor G. M. Bull** (Institute of Clinical Science, Belfast):

In treating disturbances of fluid and electrolyte balance, it is usually necessary and sometimes vital to obtain quantitative estimates of the disturbances. This is especially so in the presence of renal disease, where accurate assessment of the quantities of water and electrolytes used in treatment is often essential. Unfortunately, the techniques of medical "spacemanship", the measurement of total body water, the blood volume and body content of electrolytes are too complicated to be used in clinical practice. We have to use instead various indirect indices of the disturbances. Which indices are used is to a large extent a matter of taste. I propose to deal with those which I have found to be useful additions to the purely clinical assessment of disturbed water and electrolyte balance.

(1) *Volume packed cells (VPC) or hæmoglobin.*—When the extracellular fluid compartment is reduced in volume, the volume of packed cells and hæmoglobin concentration rise. The rise can be used as an index of underhydration. For every 2% rise in VPC over 45%, or for every 0·7 gram/100 ml. rise in hæmoglobin over 15 grams/100 ml., the patient lacks not less than 150 ml. fluid. The composition of this fluid varies in different circumstances, but generally is equivalent to $\frac{1}{2}$ to $\frac{1}{3}$ isotonic extracellular fluid.

Obviously this assessment is liable to various errors, particularly if the patient was anæmic before the onset of underhydration or has lost blood as well as other fluids during the course of his illness or operation. In practice these errors limit the use of this index in most circumstances but it is of special value as a guide to plasma or dextran therapy in burns. These plasma expanders should be given at such a rate as to maintain the VPC at a level not greater than 45%.

(2) *Plasma specific gravity.*—When the extracellular fluid compartment is reduced in

volume without loss of serum proteins, the concentration of proteins rises in the same way as the VPC. The total plasma protein concentration is very easily estimated by determining the plasma specific gravity (PSG) by the copper sulphate method (Phillips *et al.*, 1950). The normal PSG is 1·027 and for each rise of 0·001 over this figure, an adult patient lacks not less than 200 ml. of fluid. Again, the composition of this fluid will vary, but in general, because cellular and extracellular fluid are lost, the water must be accompanied by the appropriate ions for the two compartments.

It is usual to give only the extracellular ions Na, Cl and $HCO_3$ immediately, and to delay the giving of intracellular ions, particularly potassium, until later. This is because there is often a high concentration of potassium in the extracellular space in underhydration and immediate further additions may prove fatal. Time must be given for the circulation to improve so that the cell space will accept the added ions. Thus, it is usually best to administer Na-containing fluids of a strength from a half to a third of isotonic. This is done by administering bottles of 5% glucose between bottles of isotonic Na-containing fluids. The proportion of NaCl to either $NaHCO_3$ or sodium lactate (which is converted to $NaHCO_3$) administered will depend on the state of acid-base balance. KCl may be added at the rate of 2 grams per litre of infusion fluid once the urine flow exceeds 1 ml. per minute or, if possible, potassium should be given by mouth in doses of 5 to 10 grams/day.

The calculated quantity of fluid should be given rapidly and may safely be infused as fast as an ordinary intravenous set will deliver it (approximately 1 litre in 20 minutes). Once the quantity is in the body, a few minutes should be allowed for equilibrium to occur and a further sample of blood taken for PSG estimation and a reassessment of further requirements of fluid and electrolyte.

The PSG as a criterion of underhydration is subject to the same type of error as given for the volume packed cells but, as the plasma protein concentrations vary much less than the hæmoglobin and are replaced very rapidly following loss, the PSG is a much more generally useful indicator than the VPC.

(3) *Venous pressure.*—The measurement of the venous pressure is a valuable method of determining the cause of a state of circulatory inadequacy. In cardiac failure it is raised, while in the oligæmic states it is lowered. It can be measured by inspection of the neck veins when it is raised and, at all levels, can be measured by means of a venous catheter. Polythene venous catheters are very convenient routines for intravenous therapy and can be left *in situ* for many days. This has the additional advantage that during intravenous therapy the venous pressure changes can be continuously observed, using the transparent polythene catheter itself as the manometer. Indeed it should be a rule that measurements of venous pressure be made at intervals during infusions.

(4) *Carbon dioxide combining power* ($CO_2CP$).—Although estimation of the $CO_2CP$ by itself does not give a complete picture of disturbances of acid-base balance, it is sufficient for clinical purposes. In alkalæmia it is raised and in acidæmia lowered. Respiratory acidosis, in which it is also raised, can be distinguished clinically from metabolic alkalæmia because of the presence of cyanosis in the former. Respiratory alkalosis, in which the $CO_2CP$ is lowered, can be distinguished from metabolic acidæmia by the fact that latent or overt tetany can be elicited in the former, despite the fact that other clinical manifestations are similar.

The following formula may be used to calculate the quantity of base required to correct acidæmia in a normal-sized adult:

$(27-x)50$ = mEq. $NaHCO_3$ or sodium lactate required, where $x$ is the patient's $CO_2CP$.

In alkalæmia it is unnecessary to provide additional anion and it is sufficient to ensure that there is no underhydration or deficiency of potassium and sodium, particularly the former.

(5) *Serum potassium.*—In many conditions where underhydration results from loss of body fluids in vomiting or diarrhœa and also in some circumstances of renal failure patients may become severely depleted of potassium. Conversely, in other types and stages of renal disease potassium retention may occur. Unfortunately, measurement of the serum potassium and electrocardiography frequently do not reflect the body content of this ion. For example, almost any severe state of underhydration is associated with a raised or slightly raised serum potassium concentration even when the body as a whole is depleted of the ion. Despite this, a knowledge of the serum potassium concentration is important because a level above approximately 7 mEq. per litre indicates a danger of death from cardiac arrest while a level below approximately 3 mEq. per litre almost invariably indicates a deficiency of potassium. Where the blood level is abnormally high it should be lowered by administration of glucose and insulin and protection provided against the effects of the high concentration by giving calcium and sodium bicarbonate. Where a deficiency of potassium is suspected on clinical grounds or from the blood level it may be administered orally as KCl in doses of 5 to 10 grams per day or intravenously in a concentration not exceeding 2 grams per litre. Whichever route is used, it is a safe rule to avoid giving potassium unless the urine flow exceeds 1 ml. per minute.

(6) *Serum sodium.*—The level of serum sodium frequently provides a guide to the distribution of water in the various body compartments but is often a bad indicator of the quantity of sodium in the body. For example a low serum Na concentration is often present in œdema, despite the presence of an excess of Na in the body.

High levels of serum Na almost invariably indicate cellular underhydration while low levels are usually associated with cellular overhydration. Cellular underhydration is usually managed very simply by the administration of water or 5% glucose. The management of cellular overhydration will depend on the cause. Most frequently it results from sodium deficiency extracellularly and here the following formula may be used as a guide to Na requirements:

$(140-x)50$=mEq. Na required, where $x$ is the patient's serum Na concentration.

The calculated quantity of Na may be given as NaCl, $NaHCO_3$ or sodium lactate depending on the state of acid-base balance. The route of administration should be by mouth where possible or intravenously, as for example a 10% solution in other circumstances.

These simple indices provide a guide to treatment but should not be allowed to sway one's clinical judgment. The cosmetic appearance of the electrolyte block is of far less importance than the clinical state.

REFERENCE.—PHILLIPS, R. A., *et al.* (1950) *J. biol. Chem.*, **183**, 305.

**Dr. J. F. Goodwin** (London): *The Cardiographic Assessment of Electrolyte Imbalance*

Disturbances of body calcium and potassium produce characteristic cardiographic changes, which are dependent mainly upon the extracellular concentration of these electrolytes. Cardiographic changes due to hypermagnesæmia have been reported (Wacker and Vallee, 1957). Serum levels of potassium and calcium correlate roughly with the type and severity of cardiographic changes produced, but these changes are the result of a high or low concentration of the appropriate electrolyte within the heart muscle cells. If the heart muscle is already damaged by disease or under the influence of drugs, the characteristic alterations in the cardiogram may be modified or obscured. Furthermore, the serum concentration of electrolyte may not necessarily reflect the concentration within the heart, although it apparently usually does so.

(1) *Disturbances of potassium balance.*—(*a*) *Hypokalæmia:* The following changes are produced in the ventricular (QRST) complex of the cardiogram: (i) QRS amplitude increased. (ii) ST segment prolonged. (iii) Duration of systole (QT interval) prolonged. (iv) U wave increased in size. (v) ST segment depressed. (vi) T wave flattened. (vii) Arrhythmias.

The principal effects of potassium depletion are to produce a progressive increase in the duration of systole, arrhythmias, and finally arrest of the heart in systole.

The QT interval is measured from the beginning of the Q wave to the end of the T wave, and must be corrected for the heart-rate. This is usually achieved by Taran and Szilagyi's (1947) modification of Bazett's (1920) formula, so that $QT_c=QT/C$, where $QT_c$=corrected QT interval, QT=measured duration of systole and C=cycle length. The normal $QT_c$ is given as $0{\cdot}38$–$0{\cdot}39\pm0{\cdot}04$, and is a little longer in women than in men and children.

The QT interval, however, is sometimes difficult to assess owing to the development of large U waves, which may make accurate measurement impossible, or fallacious (McAllen, 1951). However, in my experience, the QT interval can often be measured, and when this is possible, correlates reasonably well with the serum potassium level. Fig. 1 shows the changes in the cardiogram with different levels of serum potassium. The sagging and prolongation of the ST segment and T wave are very characteristic in well-marked hypokalæmia, while the U wave may merge with the P wave of the next cycle or masquerade as the P wave in cases with nodal rhythm.

(*b*) *Hyperkalæmia:* The principal abnormality is in the T wave which becomes tall, spiked, and often exceeds the QRS in amplitude. When the serum potassium reaches 8·0 mEq./l. conduction defects occur, especially intraventricular block, and there is considerable risk of ventricular standstill (Fig. 1). When the serum potassium is raised, the $QT_c$ is usually in the normal range, possibly as a result of associated hypocalcæmia, except when the QRS is prolonged (Fig. 2).

(2) *Disturbances of calcium balance.*—(*a*) *Hypocalcæmia:* A deficiency of ionizable calcium results in an increase in the duration of systole, and also an increase in the duration of the ST segment (Yu, 1952). The appearances are different from those of hypokalæmia, for the ST segment is not depressed, and U waves do not appear (Fig. 3).

(*b*) *Hypercalcæmia:* The QT interval becomes short so that the ST segment virtually disappears (Fig. 3).

There are thus quite distinctive patterns in these four types of electrolyte disturbance. But the characteristic cardiographic changes may be considerably modified by the association of more than one electrolyte abnormality (such as hyperkalæmia and hypocalcæmia in uræmia),

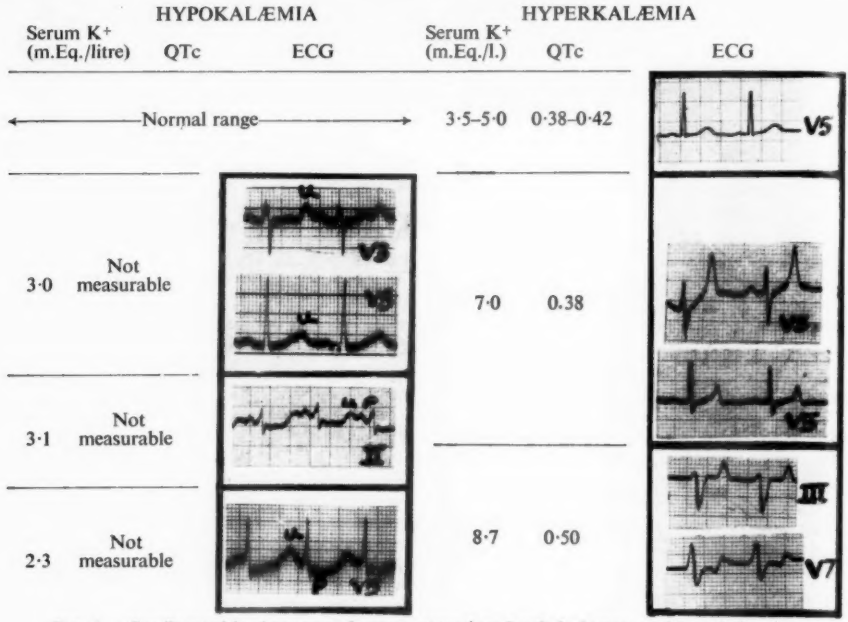



FIG. 1.—Cardiographic changes and serum potassium levels in hyper- and hypokalæmia.

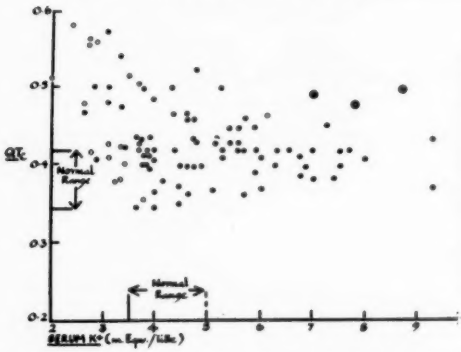



FIG. 2.—$QT_c$ of the cardiogram plotted against serum potassium levels. The closed circles represent patients who were originally hyperkalæmic. In most of these the serum potassium subsequently fell as a result of treatment. The open circles represent patients originally with hypokalæmia. There is a negative correlation between $QT_c$ and serum potassium in both groups of cases, when the serum potassium is low, but not when it is elevated. Three cases with a wide QRS complex and long $QT_c$ with a high potassium level are shown with double circles.

$r$ low $K^+ = -0{\cdot}84$. $r$ high K $= -0{\cdot}69$.

and by co-existing cardiac disease (such as cardiac infarction, left ventricular hypertrophy, and pericarditis). Thus in chronic renal failure, the cardiogram may be influenced by hyperkalæmia, hypocalcæmia, pericarditis, and left ventricular hypertrophy, and will not therefore always give an accurate picture of any single electrolyte disturbance.

In order to evaluate more accurately the contribution of the cardiogram to the assessment of electrolyte disorders I have made a personal study of 113 cardiograms from 43 patients. These have been grouped according to the type of electrolyte disturbance found, as follows:

| "Pure" electrolyte disturbance | | | "Mixed" electrolyte disturbance | | |
|---|---|---|---|---|---|
| Hyperkalæmia | .. | 24 cases | Hyperkalæmia with hypocalcæmia | .. | 2 cases |
| Hypokalæmia | .. | 13 cases | Hypokalæmia with hypercalcæmia | .. | 1 case |
| Hypercalcæmia | .. | 1 case | Hypokalæmia with hypocalcæmia | .. | 1 case |
| Hypocalcæmia | .. | 1 case | | | |

The normal values for serum potassium are 3·5–5·0, and for serum calcium 4·5–5·0 mEq./l.

*The assessment of the severity of hyperkalæmia.*—The maximum height of the T wave was measured, irrespective of the lead in which it occurred, which was usually V4, V5, or V6.

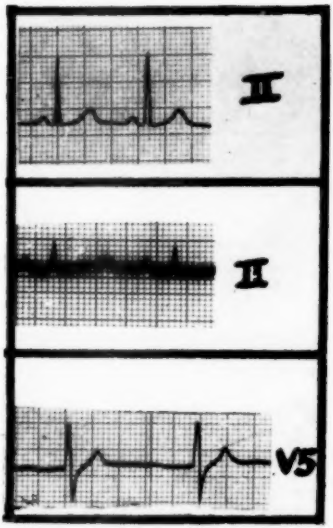
| | Serum $Ca^{++}$ (m.Eq./litre) | QTc | ECG |
|---|---|---|---|
| Normal | 4·5–5·5 | 0·38–0·42 |  |
| Hypocalcæmia | 4·0 | 0·52 | |
| Hypercalcæmia | 8·0 | 0·31 | |



FIG. 3.—Cardiographic changes and serum calcium in hyper- and hypocalcæmia.

Although the T waves were often augmented, this was not always the case. The maximum height of the T wave in health was found to be 13 mm. in a series of normal subjects studied by my former colleague Dr. O. P. Malhotra (Malhotra, 1957). In most of the hyperkalæmic cases the T waves were smaller than this, and there was a poor positive correlation between the height of the T wave and the serum potassium concentration ($r=0·58$). Thus, the level of serum potassium can only be roughly judged from the amplitude of the T waves. The shape of the T wave was often more helpful, being narrow at its base, and tapering sharply to a point. Augmented T waves from other causes, such as posterior infarction and pericarditis, tend to have a wider base, but this difference was not always reliable.

Conduction disturbances and arrhythmias were present in 12 of 24 cases. Ventricular ectopic beats appeared at serum potassium levels of 5·9–6 mEq./l., while bundle branch block was present in all cases with a level of 8·0 mEq./l. or above (Fig. 1).

Difficulties in interpretation also arose when associated cardiac lesions were present, especially acute pericarditis, and these will be discussed later.

The presence of augmented T waves is an important guide to the development of hyperkalæmia, but need not occasion immediate anxiety about the patient's safety. However, when the serum potassium rises to 8·0 mEq./l. or more, serious conduction defects appear (Fig. 1). The first sign of this dangerous situation is widening of the QRS complex, resembling bundle branch block. Nodal rhythm, or atrial standstill, is a common accompaniment and the prelude to cardiac standstill (Fig. 1). The presence of such changes calls for immediate measures to lower the serum potassium level.

*The assessment of the severity of hypokalæmia.*—The severity of the ST segment abnormality and the size of the U waves afford a rough guide to the serum potassium level, but when the $QT_c$ can be measured, this correlates inversely with the serum level, becoming longer as the level falls (Fig. 2). However, in a number of cases, the $QT_c$ cannot be measured, since the end of the T wave is obscured by the U wave. This was pointed out by McAllen (1951), who considered that prolongation of the QT interval was not commonly associated with hypokalæmia. Personal experience suggests that in the diagnosis of hypokalæmia the characteristic configuration of the ST segment, and the presence of the U waves is much more important than measurement of the QT interval. However, when this can be easily measured it is of some value in assessing alterations in the serum potassium level (Fig. 2). But the QTC is shortened by pericarditis which, if associated with hypokalæmia, may produce misleading cardiographic appearances (Fig. 4).

*Rapid changes in the serum potassium level and the cardiogram.*—When a high serum

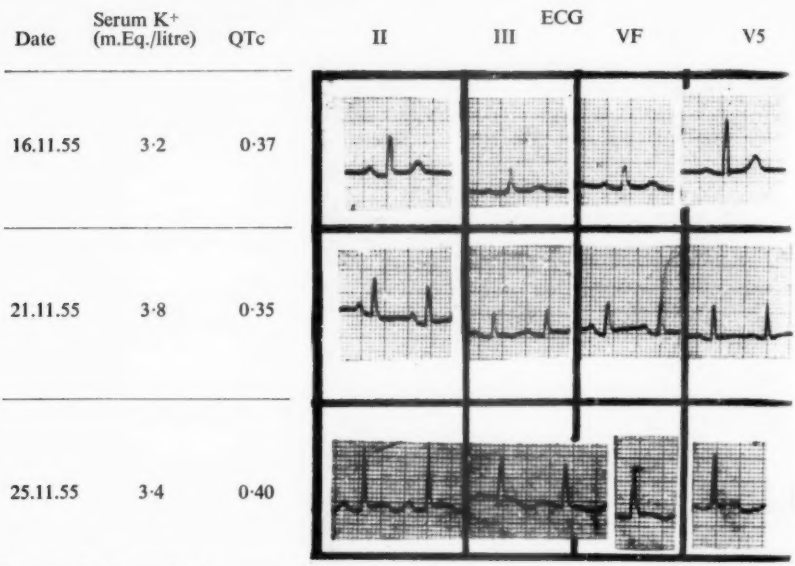



FIG. 4.—Cardiographic signs and $QT_c$ in a patient (female, aged 24) with systemic lupus, pericarditis and hypokalæmia. The $QT_c$ is shortened, owing to the pericarditis, which obscures the signs of hypokalæmia in the cardiogram of 16.11.55.

potassium is rapidly lowered by dialysis or other means, the cardiographic changes usually follow the serum potassium level, but occasionally marked discrepancies may occur, the augmented T wave of hyperkalæmia persisting even when the estimated serum potassium level has fallen to normal. This may be because there is still an accumulation of potassium in the heart muscle and probably the cardiogram in these circumstances is a better guide to the potassium balance than is the biochemical level.

*Hypocalcæmia and hypercalcæmia.*—The numbers in the series are too small to permit of any deduction on the correlation between the cardiographic appearances and the serum calcium level, but Yu (1952) has shown a good negative correlation between the length of the QT interval and of the ST segment respectively, and the level of serum calcium.

*Combined electrolyte disturbances.*—The commonest combined disorder is probably hypocalcæmia and hyperkalæmia, occurring in uræmia, in which the ionizable calcium is known to fall because of phosphate retention. In two cases in the hyperkalæmic series the serum calcium was estimated and found to be reduced, and the association of augmented T waves with a long QT interval suggested coincident hypocalcæmia (Fig. 5).

*The influence of cardiac disease on the cardiogram of electrolyte imbalance.*—Associated cardiac disease (pericarditis, cardiac infarction, hypertensive heart disease and infective endocarditis) produced confusing cardiographic appearances.

In a patient with systemic lupus, the serum potassium level was low, but the $QT_c$ was short, as a result of the pericarditis, which thus tended to obscure the changes of hypokalæmia (Fig. 4). Braun *et al.* (1951) have reported a similar case in which the signs of pericarditis obscured those of associated hypokalæmia. In the other cases with pericarditis, the serum potassium was high, and the pericarditis did not obscure the cardiographic signs of hyperkalæmia, probably because the former can produce similar tall T waves, although this did not occur in this series. Cardiac infarction caused difficulty in interpretation by partially masking the effects of severe hyperkalæmia. In one case atypical bundle branch block was associated with both posterior infarction and hyperkalæmia. The development of a wide QRS complex, and elevation of the ST segment in posterior leads raised the question of further posterior infarction, but the administration of glucose, lactate and insulin to reduce the potassium concentration caused the cardiogram to revert towards normal indicating that the changes were due to the hyperkalæmia.

In posterior infarction the præcordial T waves tend to become tall and peaked, resembling those of hyperkalæmia. These changes, which are reciprocal to posterior T-wave inversion, suggested hyperkalæmia when the reverse was actually the case (Fig. 6). The increase in

| Date | Serum $K^+$ (m.Eq./litre) | Serum $Ca^{++}$ (m.Eq./litre) | QTc |
|---|---|---|---|
| 24.12.57 | 5·4 | 3·2 | 0·45 |
| 27.12.57 | 5·3 | 3·0 | 0·50 |
| 13.1.58 | 3·7 | 4·8 | 0·44 |
| 15.1.58 | 4·6 | 5·2 | 0·45 |

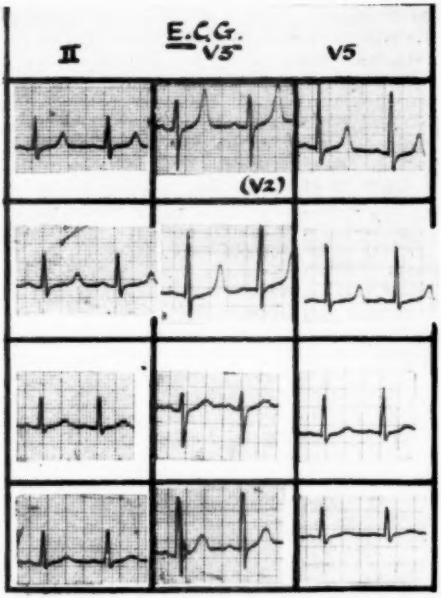



FIG. 5.—Cardiogram showing the association of pointed, augmented T waves with a long $QT_c$ in a patient (female, aged 65) with hyperparathyroidism, hyperkalæmia and hypocalcæmia, and the return to a normal configuration with restoration of normal electrolyte values. Parathyroid tumour removed 19.12.57.

| Date | Serum $K^+$ (m.Eq./litre) | QTc |
|---|---|---|
| 5.7.57 | 2·7 | 0·44 |
| 10.7.57 | 3·2 | 0·39 |

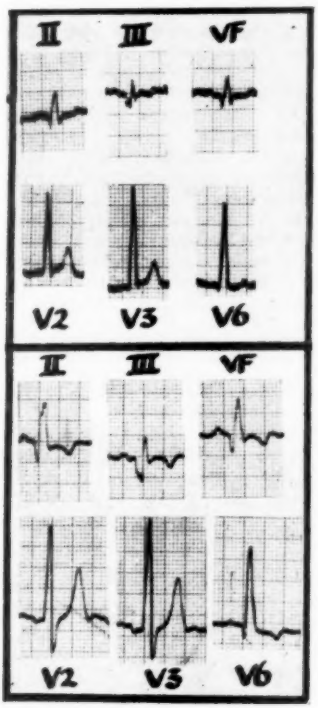



FIG. 6.—Cardiogram of a patient (male, aged 69) with old posterior cardiac infarction and ischæmic heart disease, acute tubular necrosis, and hypokalæmia. The tall T waves in chest leads are reciprocal to T-wave inversion in posterior leads and mask the signs of hypokalæmia. The QRS has become wider and the Q waves deeper in the tracing of 10.7.57, possibly as a result of further infarction.

Q waves in leads II, III, and VF and the widening of the QRS complex in the second cardiogram were compatible with further infarction. Left ventricular hypertrophy and ischæmic heart disease cause ST segment depression, and flattening or inversion of the T wave. The QT interval is usually prolonged and the changes of hypokalæmia may therefore be masked.

In one case in this series, however (a patient with hypertension due to primary aldosteronism) prolonged hypokalæmia appeared to mask the signs of left ventricular hypertrophy, which become manifest when the serum potassium was restored to normal. But hypokalæmia is well known to cause permanent myocardial necrosis and fibrosis, both in animals and in man, the degree of necrosis being proportional to the duration of the hypokalæmia (McAllen, 1955; Macpherson, 1956). Hypokalæmic necrosis may therefore have been partly responsible for the T-wave inversion in this case. In one patient tall T waves due to hyperkalæmia were suppressed by the signs of left ventricular hypertrophy. The reverse may occur, for Sharpey-Schafer (1943) showed that T waves inverted by left ventricular hypertrophy became positive after potassium administration. Conversely, according to Bellet (1955) hyperkalæmia increases the degree of T-wave inversion due to infarction. Levine *et al.* (1956) showed that hyperkalæmia could produce changes in the cardiogram suggesting cardiac infarction or pericarditis which could be abolished by reducing the serum potassium. This suggests that local cardiac electrolyte disturbance may cause myocardial disturbance sufficient to produce currents of injury. Permanent damage to the myocardium from hyperkalæmia has not been reported, perhaps because prolonged severe hyperkalæmia is incompatible with life.

*Digitalis and potassium deficiency.*—The cardiographic signs of hypokalæmia may be difficult to detect in the presence of marked digitalis effects upon the ST segment and T wave. It is important to realize this, for potassium deficiency potentiates the toxic effects of digitalis on the ventricular myocardium, and dangerous or fatal ventricular arrhythmias can occur in patients who are taking full doses of digitalis and then become depleted of potassium as a result of diuretic therapy. It is wise, therefore, to give potassium supplements by mouth to patients receiving digitalis and diuretics, especially chlorothiazide, which can cause considerable loss of potassium in the urine. In a personal case, a patient receiving digitalis and chlorothiazide without potassium supplements for heart failure had frequent short bursts of ventricular tachycardia. The serum potassium was 3·2 mEq./l., but the signs of potassium deficiency on the ST segment of the cardiogram were obscured by the digitalis effects, atrial fibrillation, and by right bundle branch block due to the cardiac lesion.

## Summary and Conclusions

The cardiogram is a good rough guide to the extracellular concentration of potassium and calcium. It is more useful than biochemical measurements in predicting dangerously low or high potassium levels. The cardiogram may be misleading in the presence of combined electrolyte disturbances, and of associated cardiac disease, especially cardiac infarction and left ventricular hypertrophy. Electrolyte disturbances may themselves counterfeit cardiac disease. The best guide to hypokalæmia is the characteristic deformity of the ST–T segment, the presence of U waves, and the prolongation of the QT interval when this can be measured. Hyperkalæmia can be quantitated roughly by the height and shape of the augmented T waves, and by disturbances of conduction.

Hypocalcæmia and hypercalcæmia can usually be diagnosed without difficulty. The ST and QT intervals are lengthened in the former and shortened in the latter, without abnormality of the ST segment or T wave. Cardiographic signs of hypokalæmia may be difficult to detect in the presence of digitalis effects, and the tendency for hypokalæmia to potentiate dangerous digitalis arrhythmias is of great importance.

## Acknowledgments

I am grateful to my colleagues in the Departments of Medicine and Surgery at the Postgraduate Medical School for allowing me to study their patients, and to Professor E. J. King and Dr. Ian Wootton, of the Department of Biochemistry, Postgraduate Medical School, for allowing me to quote the results of their electrolyte estimations.

## REFERENCES

Bazett, H. C. (1920) *Heart*, **7**, 353.
Bellet, S. (1955) *Arch. intern. Med.*, **96**, 618.
Braun, K., Fryd, C. H., and Liban, E. (1951) *Cardiologia*, **18**, 244.
Levine, H. D., Wanzer, S. H., and Merrile, J. P. (1956) *Circulation*, **13**, 29.
McAllen, P. M. (1951) *Brit. Heart J.*, **13**, 159.
—— (1955) *Brit. Heart J.*, **17**, 5.
Macpherson, C. R. (1956) *Brit. J. exp. Path.*, **37**, 279.
Malhotra, O. P. (1957) Unpublished data.
Sharpey-Schafer, E. P. (1943) *Brit. Heart J.*, **5**, 80.
Taran, L. M., and Szilagyi, N. (1947) *Amer. Heart J.*, **33**, 14.
Wacker, W. E. C., and Vallee, B. L. (1957) *New Engl. J. Med.*, **257**, 1254.
Yu, P. N. G. (1952) *Amer. J. med. Sci.*, **224**, 413.

# Section of Epidemiology and Preventive Medicine

President—IAN TAYLOR, M.D., M.R.C.P., D.P.H.

[*February* 21, 1958]

## SYMPOSIUM ON EPIDEMIOLOGICAL RISKS OF ANTIBIOTICS

**Dr. E. J. L. Lowbury** (Medical Research Council Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital): ***Hospital Infection***

The rise of antibiotic-resistant bacteria, especially in hospitals, has led to some apprehension about the future of chemotherapy. A glance at the Registrar-General's Statistical Review of England and Wales since 1925 (Fig. 1) is reassuring, for it shows that the death-rate from infective diseases—and from their chief representative, tuberculosis—has continued to fall, and with less fluctuation than before. But it is obvious that many factors have contributed to this fall, and there is nothing in the collective record which clearly indicates the contribution—or exhaustion—of the antibiotics[1]; the downward trend was, in fact, present before

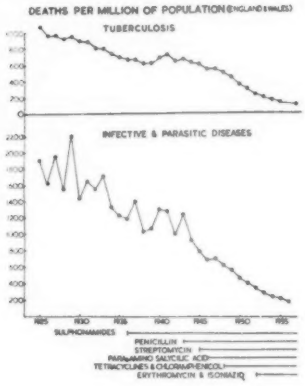



FIG. 1.

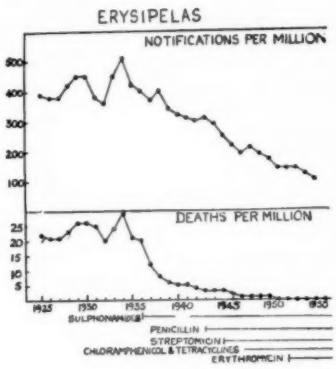



FIG. 2.

the arrival of the sulphonamides. If, however, we plot the deaths and notifications in respect of erysipelas over the same period (Fig. 2), this disease is shown to have become less lethal and also less common since the arrival of the sulphonamides. A number of other relevant diseases (e.g. puerperal pyrexia, meningococcal infection, osteomyelitis) show in the same period a striking fall in death-rate which for various reasons is not always accompanied by a fall in notifications. For some infections (e.g. the pneumonias, which are not classified with infective diseases) the death-rate has not fallen dramatically, and deaths from bronchopneumonia have, if anything, become a little more common since 1946. But the Registrar-

[1] I use the word "antibiotic" to include all antibacterial drugs which can be administered by systemic routes.

General's Review tells us little or nothing about those infections against which the antibiotics have suffered their biggest reverse; I mean hospital infections with *Staphylococcus aureus* and Gram-negative bacilli in which the emergence and spread of resistant strains have been of special importance.

Drug resistance was described as long ago as 1887, and Ehrlich recognized its dangers. Soon after the arrival of the sulphonamides, resistance became a familiar problem in the treatment of streptococcal, gonococcal and other infections; the emphasis (as later with streptomycin) was on strain variation and on the emergence of resistance under treatment. With the increasing use of penicillin a new phenomenon was revealed in the mid-1940s by North and Christie (1945) and by Mary Barber and her colleagues (1948), and amplified by many workers in the years that followed. Briefly, staphylococci carried by patients and staff in hospitals were shown to reflect the use there of antibiotics—of penicillin, streptomycin, tetracycline and, more recently, erythromycin; the hospital flora differed from the nasal staphylococci of the general population also in showing a preponderance of strains belonging to phage group III. It was shown that cross-infection plays a major role in producing this state of affairs.

These ecological adjustments of the staphylococci have had important clinical consequences. Howe (1954) and Blowers and his colleagues (1955) have quoted increases in the incidence of post-operative sepsis during recent years, the infections being due usually to antibiotic-resistant staphylococci and associated with the increase in their numbers. There have been many outbreaks of staphylococcal sepsis in maternity wards. Advances (e.g. in chest surgery) which were made possible by antibiotics have been jeopardized by the break-through of organisms resistant to all available drugs. Some of the blame may, as McDermott (1956) points out, be attributed to inadequate resistance in patients kept alive by other forms of treatment; but there is also evidence to show that some staphylococci selected by antibiotic therapy (especially those of phage type 80) have enhanced virulence and communicability (Rountree and Freeman, 1955). Such facts have made it necessary to reconsider the indications for antibiotic therapy, especially in hospital, and also to discover ways of preventing the emergence of resistant variants and expelling those which have appeared.

The difficulty of preventing cross-infection in a burns unit is notorious. In the Birmingham Accident Hospital burned patients occupy two wards of an old-style hospital. Some control of cross-infection has been achieved by the use of a plenum-ventilated dressing station and other prophylactic measures especially against *Streptococcus pyogenes* (Colebrook, 1950). In recent years the need to accommodate a larger number of patients has made it difficult to maintain all the barriers against cross-infection at full efficiency; and since tetracycline and erythromycin, rather than penicillin, have had to be used for the therapy of streptococcal infection (Lowbury and Cason, 1954), there has been an abundance of staphylococci resistant to these antibiotics in the burns; *Strep. pyogenes* has also been found resistant to tetracycline and, occasionally, to erythromycin (but never to both).

In Fig. 3 I have tried to show what association exists between the use of these two antibiotics (shaded areas) and the proportion of resistant strains in the burns wards during 1955, 1956 and 1957. It represents only a sampling—20 strains of *Staph. aureus* from consecutive patients swabbed at the beginning of each month plotted on the same scale as the average number of patients per day treated with the antibiotics in the last week of the previous month. In the middle of 1956 we found an increasing incidence of tetracycline-resistant streptococci, and therefore replaced tetracycline by erythromycin as our routine antibiotic for streptococcal infections. After that time tetracycline-resistant staphylococci became less common, but erythromycin-resistant staphylococci increased in numbers. In spite of the restricted sampling, there was a considerable association between the rise and fall of resistant staphylococci and the

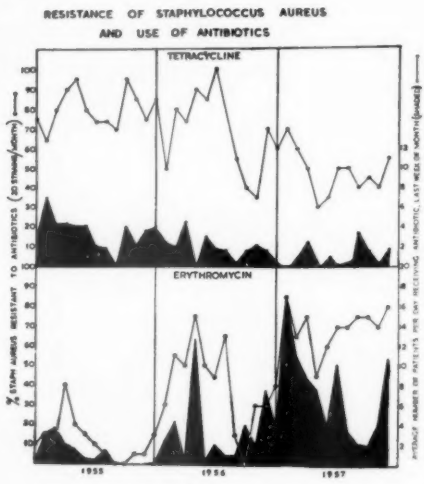



FIG. 3.

varying use of erythromycin, in particular, from month to month. It is tempting to infer from this that resistant organisms can be expelled from a ward readily enough merely by withholding the antibiotic in question; but our experience with novobiocin suggests that it is unsafe to generalize on these lines. A trial of novobiocin therapy in 1956 led to the emergence of a large proportion of novobiocin-resistant staphylococci. Fig. 4 shows the position as it stood at the end of the trial (in January 1957) and for the remainder of that year; weekly resistance rates for *all* strains of *Staph. aureus* are plotted here. During the five months after the trial there was a fall to zero, followed by a prompt return of resistant staphylococci on resumption of novobiocin therapy for a few patients in July. After this, however, there was no decline in the small incidence of novobiocin-resistant staphylococci, in spite of the fact that the antibiotic was not being used: this may have been due to the prolonged stay in the Burns Unit of certain carriers of novobiocin-resistant staphylococci.

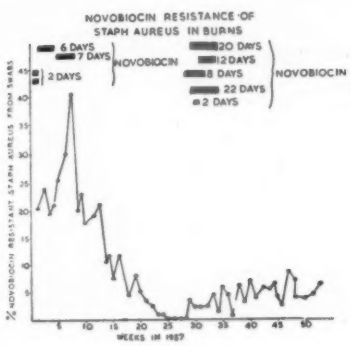



FIG. 4.

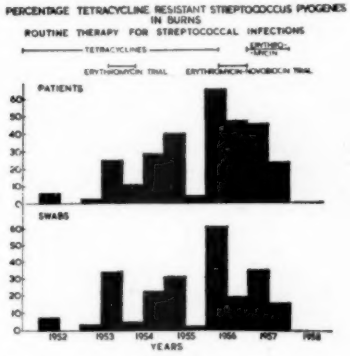



FIG. 5.

*Strep. pyogenes* is still the most important pathogen commonly found on burns in hospital, as it is much more liable than other bacteria to cause the failure of skin grafts. It is more vulnerable than *Staph. aureus* to the antibiotics; indeed, true penicillin resistance is unknown. But we have found an increasing incidence of tetracycline-resistant streptococci, and recently erythromycin-resistant strains have appeared. Fig. 5 shows the proportion of tetracycline-resistant streptococci isolated in six-month periods since 1952 (before which all strains were sensitive). It shows a mounting incidence and suggests the establishment of a "hospital streptococcus". Serological studies have shown that a number of different types are represented among these tetracycline resisters; e.g. the predominant strain in 1955 was of type 9, and in 1957 it was of type 5/11 and related patterns (which have been the commonest to show resistance). Erythromycin resistance appeared in streptococci of two types (3 and 14). It would appear that resistant mutants of *Strep. pyogenes* have emerged on a number of occasions. This view is supported by the multiplicity of types, and by the appearance, after treatment, of streptococci of the same types as those of sensitive strains isolated before treatment—a phenomenon we have also observed repeatedly in the case of *Staph. aureus*. But since there is no appreciable increase in the frequency of streptococcal infections between 1952 and 1957, it appears likely that resistant strains have to some extent become endemic and one may with reason speak of a "hospital streptococcus".

There are two approaches by which we can attempt to combat these evils: (1) by aiming to prevent the emergence of resistant variants, and (2) by using methods to prevent their spread. Of the former, combined therapy with two or more agents has had most attention and has been successful against tuberculosis. Our experience during a trial in which novobiocin was used only in combination with erythromycin was somewhat disappointing; in spite of the therapeutic effectiveness of this mixture, about 20% of doubly resistant staphylococci appeared after three months of the trial (Lowbury, 1957). The use of antibiotics in rotation—and with economy—may perhaps be more effective. Our best hopes probably lie in the development of agents which, like bacitracin, neomycin, chlorhexidine and vancomycin against *Staph. aureus* and polymyxin against *Ps. pyocyanea*, never, or hardly ever, select variants which are resistant and capable of causing infection. But until (and perhaps even after) we are supplied with the ideal therapeutic compounds of this kind, the most profitable line of attack is, undoubtedly, to improve aseptic discipline and to block the lines of bacterial communication.

REFERENCES

BARBER, M., and ROZWADOWSKA-DOWZENKO, M. (1948) *Lancet*, ii, 641.
BLOWERS, R., MASON, G. A., WALLACE, K. R., and WALTON, M. (1955) *Lancet*, ii, 786.
COLEBROOK, L. (1950) A New Approach to the Treatment of Burns and Scalds. London.
HOWE, C. W. (1954) *New Engl. J. Med.*, 251, 411.
LOWBURY, E. J. L. (1957) *Lancet*, ii, 305.
——, and CASON, J. S. (1954) *Brit. med. J.*, ii, 914.
MCDERMOTT, W. (1956) *Brit. med. J.*, ii, 837.
NORTH, E. A., and CHRISTIE, R. (1945) *Med. J. Aust.*, ii, 44.
ROUNTREE, P. M., and FREEMAN, B. M. (1955) *Med. J. Aust.*, ii, 157.

**Dr. J. B. Selkon** (Medical Research Council's Group for Research on Drug Sensitivity in Tuberculosis, Post-graduate Medical School of London):

*Tubercle Bacilli in the Community*

Between June 1955 and March 1956 the Medical Research Council's Tuberculosis and Statistical Research Units and the Group for Research on Drug Sensitivity in Tuberculosis carried out in Great Britain a national survey of the incidence of drug-resistant strains of tubercle bacilli in newly diagnosed cases of pulmonary tuberculosis (Fox *et al.*, 1957; Mitchison and Selkon, 1957). In order that the findings should permit an unbiased estimate of the prevalence of drug-resistant infections in the whole of Britain, 80 clinics were randomly selected. These clinics supplied sputum specimens from 1,404 patients, which comprised a third of the total number of previously untreated patients diagnosed during that time.

Patients eligible for this study were defined as those with newly diagnosed and previously untreated pulmonary tuberculosis, aged 15 years and over, producing sputum and normally resident in the clinic area. An early morning specimen of sputum was sent to the central laboratory (M.R.C. Group for Research on Drug Sensitivity in Tuberculosis) and to the local laboratory, before treatment was started.

Of the 1,404 patients included in the survey, 60 were later diagnosed as not suffering from tuberculosis, leaving 1,344 newly diagnosed patients. Bacteriological confirmation was obtained on 974 at the central laboratory, and on a further 172 at the local laboratories. In the remaining 198 patients the diagnosis was made on clinical grounds alone. Of 1,344 patients 63·7% were males and 36·3% females. Whereas 68·1% of the male patients were 35 years or older, 63·9% of the female patients were under 35 years of age.

TABLE I.—PREVALENCE OF PRIMARY DRUG RESISTANCE IN DIFFERENT AREAS

| Area | Total strains isolated | Resistant strains No. | Resistant strains % |
|---|---|---|---|
| London and South East* | 187 | 9 | 4·8 |
| Birmingham† | 159 | 4 | 2·5 |
| Manchester† | 106 | 8 | 7·5 |
| Liverpool† | 73 | 6 | 8·2 |
| Rest of England | 218 | 8 | 3·7 |
| Wales | 62 | 1 | 1·6 |
| Scotland | 169 | 14 | 8·3 |
| Great Britain | 974 | 50 | 5·1 |

*The 4 Metropolitan Regional Hospital Board areas.
†The Birmingham, Manchester and Liverpool Regional Hospital Board areas.

The data on drug resistance is based on the 974 positive cultures obtained at the central laboratory. Of these 974 positive cultures, 924 (94·9%) were sensitive to streptomycin, PAS and isoniazid and 50 (5·1%) were resistant to one or more of these three antituberculous drugs. Of the 50 resistant strains, 44 were strains of *Myco. tuberculosis* var. *hominis* or *bovis*, the remaining 6 being other mycobacteria, one an avian strain. Of the 44 strains of *Myco. tuberculosis* 22, i.e. 2·3% of the positive cultures, were resistant to streptomycin, 21 i.e. 2·2%, were resistant to PAS, and 7, i.e. 0·7%, were resistant to isoniazid. 5 strains (0·5%) were resistant to more than one drug, 1 being resistant to all three. This accounts for the total of 50 instances of resistance amongst 44 strains. It is possible from these figures to say that at the time of the survey the prevalence of primary streptomycin resistance is unlikely to have been less than 1·5% or greater than 3·3%. The corresponding limits for PAS resistance are 1·5% and 3·1% and for isoniazid resistance 0·3% to 1·4%.

The geographical distribution of the 974 patients with positive cultures, and of those with resistant strains, is shown in Table I. The prevalence of resistant strains was above the national average of 5·1% for the Manchester (7·5%) and Liverpool (8·2%) areas and for Scotland (8·3%). Wales showed a very low prevalence of drug-resistant strains (1·6%). The number of resistant strains, however, is small, and these differences may therefore be no more than chance fluctuations.

Table II gives the age and sex distribution of the 974 patients whose sputum yielded a positive culture at the central laboratory and of the 50 of these who were infected with drug-resistant organisms. The prevalence of resistant strains was 3·8% among male patients and 7·7% among females. This contrast in prevalence was particularly marked under the age of 35, where 3·0% of males as compared to 9·3% of females had resistant strains. Each of these differences is statistically significant at the 5% level. This higher incidence of infections with drug-resistant organisms in females under the age of 35 is of particular interest. Their proportion of tuberculous contacts was similar to that for the men and older women and so was their proportion of home contacts. One cannot therefore explain this difference as due to more frequent or closer contact with patients excreting drug-resistant organisms. A possible explanation which would link this up with the difference in incidence of clinical pulmonary tuberculosis between the sexes in this age group is that the clinical manifestation of pulmonary tuberculosis in young women is more frequently due to recent exogenous infection than is the case in men or in older women. In men or in older women, clinically manifest disease may more frequently be due to previous latent infection. The prevalence of infection with drug-resistant organisms may therefore be much higher than our figure of 5·1% for clinically manifest disease. If this explanation is correct, it can therefore be expected that the prevalence of drug-resistant organisms in future manifest disease in men and in older women will approximate, or even be higher than, that found for young females in this survey.

TABLE II.—RESISTANCE BY AGE AND SEX

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Total | Resistant | | Total | Resistant | |
| Age | strains | No. | % | strains | No. | % |
| 15–34 | 199 | 6 | 3·0 | 216 | 20 | 9·3 |
| 35+ | 436 | 18 | 4·1 | 123 | 6 | 4·9 |
| Total | 635 | 24 | 3·8 | 339 | 26 | 7·7 |

In order to obtain information on the possible sources of infection with these drug-resistant strains, intensive contact histories were taken from the patients infected with these strains and from control patients infected with sensitive strains, chosen and individually matched according to age, sex and area of residence. Table III summarizes the contact histories of the resistant and the sensitive control patients. Of the 22 patients infected with streptomycin-resistant strains, 13 were known to have been in contact with patients who had received streptomycin. In comparison only 6 of the 22 matched control patients knew of a similar

TABLE III.—PATIENTS INFECTED WITH RESISTANT STRAINS, AND THEIR MATCHED CONTROLS WITH SENSITIVE STRAINS, SUBDIVIDED ACCORDING TO THE POSSIBLE SOURCE OF TUBERCULOUS INFECTIONS THROUGH CONTACT

| | Sensitivity status of patients in survey | | | | | |
|---|---|---|---|---|---|---|
| | Streptomycin | | PAS | | Isoniazid | |
| Status of source of infection | Resistant patients | Sensitive controls | Resistant patients | Sensitive controls | Resistant patients | Sensitive controls |
| No known chemotherapy with relevant drug .. | 9* | 16 | 9 | 18 | 4 | 7 |
| Chemotherapy with relevant drug; sensitivity not known .. .. | 10 | 6 | 7† | 3 | 1 | 0 |
| Resistant to relevant drug | 3 | 0 | 5 | 0 | 2 | 0 |
| Total patients or controls | 22 | 22 | 21 | 21 | 7 | 7 |

*One patient lived in a common lodging house frequented by a number of treated tuberculous patients.

†One patient was a laboratory technician examining the sputa of tuberculous patients receiving chemotherapy.

contact. For 3 of the 13 patients, the source case was known to have had streptomycin-resistant organisms, compared with none in the control group. For PAS resistance, 12 of the 21 patients had been in known contact with patients previously treated with PAS compared with 3 in the sensitive control group. 5 of the PAS-resistant group had been in contact with patients known to have had PAS-resistant organisms, but none of the controls. The figures for isoniazid resistance, though smaller, similarly suggest that those in contact with patients who had received isoniazid, or who were excreting resistant organisms, were more likely to be infected with resistant organisms than patients not similarly exposed.

REFERENCES

FOX, W., WIENER, A., MITCHISON, D. A., SELKON, J. B., and SUTHERLAND, I. (1957) *Tubercle, Lond.*, **38**, 71.

MITCHISON, D. A., and SELKON, J. B. (1957) *Tubercle, Lond.*, **38**, 85.

**Dr. H. Williams Smith** (The Animal Health Trust, Stock, Essex):

*Drug-resistant Bacteria in Domestic Animals*

There is little doubt that the diseases of human beings in which antibiotic-resistant strains of bacteria are the most troublesome are those caused by *Staphylococcus aureus* and *Mycobacterium tuberculosis*.

The position in veterinary medicine is quite different. Tuberculosis is, of course, a very serious disease of cattle but it is controlled in Britain by the tuberculin testing of herds with the elimination of all cattle giving a positive reaction. Progress has been so satisfactory that it is hoped that within a few years all our cattle population will be virtually tubercle-free. *Staph. aureus* does cause an appreciable amount of bovine mastitis but this form of mastitis does not respond well to the intramammary injection of antibiotics—the only really satisfactory method of treating most cases of mastitis. Consequently, an increase in the proportion of resistant strains of *Staph. aureus* associated with this disease would not be so serious as it might appear at first sight. Nevertheless the proportion of penicillin-resistant strains has definitely increased. Tee (1957) found that the proportion of pencillin-resistant *Staph. aureus* cultures isolated from herd samples of milk had increased from 11% in 1954 to 47% in 1956. It would be incorrect to assume that this increase has resulted directly from the use of penicillin in treating staphylococcal mastitis. It is largely an indirect result of its widespread use in the treatment of *Streptococcus agalactiæ* mastitis. Antibiotics have been used more in the treatment of this very common condition than in the treatment of all other diseases of animals put together. Some authorities are of the opinion that about 1½ million million units of penicillin are used every year in Britain for treating mastitis. Whatever the actual amount is, it is so great that the extent to which it is present in bulk milk is such as to give concern to those interested in public health and the manufacture of dairy products. Other drugs such as streptomycin, the tetracyclines, chloramphenicol and the sulphonamides, are employed to a much lesser extent. Except in severe acute cases, drugs are given by the intramammary route only. Usually, clinical cases only are treated but, sometimes, all the cows in a herd may be treated in the hope of eradicating infection from the herd. Despite this exhibition of drugs on the grand scale, no resistant strains of *Strep. agalactiæ* have ever been reported and it appears unlikely now that any ever will be.

The bacterial species that presents the greatest veterinary problem from the point of view of drug resistance is probably *Bacterium coli*. This bacterium is usually only associated with disease in the very young and, since young farm animals receive less care and attention than young human beings, it is not surprising that *B. coli* is much more important from the veterinary than from the human point of view. This organism has an important association with a diarrhœa in young calves that is commonly called white scours, a disease that kills 5%–10% of all the calves born in Britain. A somewhat similar disease causes serious losses in piglets. Certain strains of *B. coli* are also associated with a disease of pigs called bowel œdema. The more modern chemotherapeutic agents are commonly employed in the treatment of these diseases and it is not surprising, therefore, that the emergence of drug-resistant strains of *B. coli* would be a matter of some concern to veterinary surgeons.

Our first impression that the numbers of drug-resistant *B. coli* associated with animal disease were, in fact, increasing, was gained by comparing the results of testing the drug sensitivities of strains of *B. coli* found to be associated with cases of white scours in calves in 1951–53 with those obtained in a similar survey carried out in 1955 (Smith and Crabb, 1956*a*); a greater proportion of resistant strains were found in the second survey than in the

first. Studies on the dynamics of the emergence of resistant *B. coli* in animals under treatment were then performed employing phage typing for classifying strains of *B. coli* (Smith and Crabb, 1956*b*) and a plate method for sensitivity testing (Smith and Crabb, 1956*a*; Smith, 1958). The plate method consisted simply of rubbing a rectal swab over a plate of MacConkey agar, applying paper discs containing different drugs and then incubating at 37°C. The plates could be read in six to eight hours.

The results with calves suggested that when a dominant drug-resistant *B. coli* intestinal flora emerged, it usually did so as a consequence of the depression of the multiplication of the sensitive strains accompanied by their replacement by resistant strains previously present in very small numbers only. However, in a small number of cases treated with either streptomycin or chloramphenicol, the available evidence suggested that the resistant *B. coli* arose from mutation of sensitive strains (Smith, 1958).

*In vitro* it was possible to make strains of *B. coli* of white scours origin permanently resistant to streptomycin, chloramphenicol and sulphadimidine both singly and multiply. Despite continuous efforts for six months it was not possible to make strains of *B. coli* resistant to either the tetracyclines or Furamazone.

Very few resistant strains of *B. coli* were found in the fæces of calves from self-contained herds in which drugs had never been used. The position in herds in which they had been used frequently was quite different. A close relationship existed between the drugs used in these herds and the resistance of the predominant *B. coli* intestinal flora in the calves in them. For example, in a herd where streptomycin had been used frequently, the predominant *B. coli* in the fæces of the scouring calves in this herd that had not responded to this form of treatment were streptomycin-resistant; these resistant strains had also spread to untreated calves in these herds. In many of the herds, as a result of sensitivity tests, it was possible to suggest replacing an ineffective drug with an effective one. However, unless other measures were taken to reduce the incidence of scours and hence the number of calves requiring treatment, a position was soon reached when the new drug also became ineffective. Multiple resistance was a serious position in such herds. In some of them the predominant *B. coli* fæcal flora were resistant to streptomycin, the tetracyclines, chloramphenicol and the sulphonamides.

Apart from the therapeutic use of drugs, the continuous feeding of animals on diets containing low levels of some of these agents has also had a profound effect on the emergence of resistant strains of *B. coli*. The tetracyclines in levels of 10–100 grams per ton of food are the agents most commonly used, the purpose of which, of course, is to stimulate the growth of the animals to which they are fed. I should estimate that about 50% of all the pigs in Britain are so fed and that nearly all unweaned piglets have access to food containing tetracyclines. Most of the broiler chickens, but very few of the other classes of poultry, are fed diets containing either tetracyclines, penicillin or both.

Examination of pigs and poultry kept on many different farms showed that the *B. coli* in the fæces of tetracycline-fed animals were predominantly tetracycline-resistant, while those in the fæces of animals on farms where tetracycline feeding was not practised were predominantly tetracycline-sensitive (Smith and Crabb, 1957). In some herds in which tetracycline feeding was just being introduced it was possible to trace the change of the *B. coli* fæcal flora from tetracycline-sensitive to tetracycline-resistant. In other herds tetracycline feeding was discontinued after being practised continuously for two to three years. Tetracycline-resistant *B. coli* still formed the mass of the *B. coli* fæcal flora of animals in these herds for several months afterwards. A survey of pigs entering a bacon factory revealed that the *B. coli* in the fæces of 36% of them were all tetracycline-resistant; this is probably a fairly reliable indication of the effect of tetracycline feeding on the pig population in general.

The piglets of tetracycline-fed sows quickly acquired from their mothers a *B. coli* intestinal fæcal flora that was predominantly tetracycline-resistant. Needless to say, any diarrhœa associated with *B. coli* that occurred in these piglets was not amenable to treatment with tetracyclines. Other drugs that were much more expensive, more difficult to administer and/or to which *B. coli* quickly became resistant, had to be employed instead.

The emergence of resistant strains belonging to bacterial species that are usually drug-sensitive during antibiotic feeding is not confined to *B. coli*. Under certain conditions we have found a somewhat similar state of affairs to apply, for example, in the case of *Clostridium welchii*.

## REFERENCES


Smith, H. W. (1958) *Vet. Rec.*, **70**, 575.

——, and Crabb, W. E. (1956*a*) *Vet. Rec.*, **68**, 274.

——, —— (1956*b*) *J. gen. Microbiol.*, **15**, 556.

——, —— (1957) *Vet. Rec.*, **69**, 24.

Tee, G. H. (1957) *Mon. Bull. Minist. Hlth. Lab. Serv.*, **16**, 141.

## BOOKS RECEIVED FOR REVIEW

**Bignall (J. R.),** ed. Carcinoma of the lung. Vol. I: Monographs on neoplastic disease at various sites. General editor: D. W. Smithers. pp. xii + 298. Edinburgh and London: Livingstone. 55s. 1958.

**Bishop (W. J.),** ed. Bibliography of international congresses of medical sciences. Prepared under the auspices of the C.I.O.M.S. pp. xxii + 238. Oxford: Blackwell. 25s. 1958.

**British Postgraduate Medical Federation.** Lectures on the scientific basis of medicine. Vol. 6, 1956–57. pp. ix + 393. University of London: Athlone Press. 45s. 1958.

**Butterworth.** Medical publications. London. 1958.

**Darzins (E.).** The bacteriology of tuberculosis. pp. xi + 488. Minnesota University Press. London: Oxford University Press. 80s. 1958.

**de Wardener (H. E.).** The kidney. pp. viii + 338. London: Churchill. 45s. 1958.

**Ferguson (T.).** Scottish social welfare 1864–1914. pp. xi + 609. Edinburgh and London: Livingstone. 42s. 1958.

**Foote (R. R.).** The physical treatment of varicose ulcers. pp. xii + 125. Edinburgh and London: Livingstone. 15s. 1958.

**Francis (R. S.),** and **Curwen (M. P.).** Major surgery for pulmonary tuberculosis. pp. x + 96. London: Staples. 12s. 6d. 1958.

**Houston (J. C.),** and **Stockdale (M.).** Principles of medicine and medical nursing. pp. ix + 198. London: English Universities Press. 15s. 1958.

**Ling (T. M.),** and **O'Malley (C. J. S.),** eds. Rehabilitation after illness and accident. pp. vii+119. London : Baillière, Tindall & Cox. 12s. 6d. 1958.

**McMichael (J.),** ed. Circulation. Proceedings of the Harvey Tercentenary Congress. pp. xxiii + 503. Oxford: Blackwell. 50s. 1958.

**Mayo Clinic and the Mayo Foundation.** Collected papers. Vol. 49, 1957. pp. viii+778. Philadelphia and London : Saunders. 91s. 1958.

**Medical Annual 1958.** 76th issue. Edited by Sir Henry Tidy and R. Milnes Walker. pp. xl + 580 + 23. Bristol: John Wright. 42s. 1958.

**Medical Research Council.** The determination of the ABO and Rh(D) blood groups for transfusion. pp. vi + 46. London: H.M.S.O. 3s. 6d. 1958.

**Morris (N. F.),** and **Browne (J. C. McC.),** eds. A symposium on non-toxæmic hypertension in pregnancy. pp. xii + 243. London: Churchill. 35s. 1958.

**Patey (D. H.),** ed. An introduction to surgery. pp. xi + 228. London: Lloyd-Luke. 17s. 6d. (Students' edition, 9s. 6d.) 1958.

**Perkins (G.).** Fractures and dislocations. pp. viii + 363. University of London: Athlone Press. 57s. 6d. 1958.

**Sherlock (S.).** Diseases of the liver and biliary system. 2nd ed. pp. xvi + 713. Oxford: Blackwell. 57s. 6d. 1958.

# Section of Surgery

President—A. DICKSON WRIGHT, M.S., F.R.C.S.

[*April* 2, 1958]

## The Post-auricular Wolfe Graft and Its Use in the Treatment of Malignant Ulceration of the Face

By J. C. M. CURRIE, M.B., B.Chir. (for ALAN HUNT, M.Ch.)
*London*

PRIMARY or recurrent malignant lesions of the face are usually small but require wide excision. If primary suture of such wounds is attempted, the eyelids, lips, or nostrils may be distorted. As a result, there is a temptation to skimp the excision. The post-auricular Wolfe graft enables the excision to be complete and healing to occur without deformity. The operation can be done quickly and satisfactorily under local analgesia as an out-patient.

Free full-thickness skin grafting was not an established technique until 1875, when Wolfe published the results of his experiments. Prior to this, though full-thickness skin grafting had been frequently attempted, it was rarely successful and then only with small-size grafts. The failures were due to the fact that fat retained on the deeper surface of the graft prevented it from taking (Lawson, 1870; Wolfe, 1884).

Early in his studies of ophthalmic surgery Wolfe questioned the usefulness of the pedicle graft as then practised for the correction of ectropion. The donor site always left a granulating area to scar, and if the flap died the resulting deformity was worse than the original condition. The pinch-graft method of skin grafting introduced by Reverdin in 1869 was successful, but the cosmetic results poor. However, it was while carrying out pinch grafting that Wolfe made his fundamental observation upon which he based his operation (Wolfe, 1884). Upon these observations all free full-thickness skin grafting is based, and an operation which had previously been very uncertain in its results became an established method of replacing skin loss. To-day it remains the operation of choice in grafting the eyelids, but is rarely practised elsewhere. We think that the Wolfe graft has a place in the treatment of skin loss elsewhere—especially in the region of the face. With the use of post-auricular skin it becomes a remarkably simple operation. The donor area heals as a linear scar and presents no problems.

In the region of the face the patient will, and has a right to, judge the success of an operation by the resulting cosmetic appearance. A full-thickness graft contains all the dermal elements and once established behaves like normal skin. The appearance is natural, it rarely contracts, usually remains supple, and stands up to wear and tear. Moreover, the donor skin matches closely the surrounding skin in colour and texture. To replace face skin, face skin is obviously best, but skin from the post-auricular groove is virtually identical.

Skin from the mastoid process and the posterior surface of the auricle had been used previously, but it was not until after the First World War with its impetus to plastic surgery that the advantages of skin from the post-auricular groove itself were appreciated. This skin was first used on a pedicle by Lyons Hunt (1926). He was followed by Blair (1932) and Wheeler (1936) and later by many others, who used free grafts from this mainly to reconstruct eyelids. Since the post-auricular skin overlies two firm structures, bone and cartilage, the graft can be taken easily and free from underlying fat. Having taken the graft, the raw area is readily closed. The only disadvantage is that a piece of skin greater in width than 2·5 cm. can rarely be obtained. The usual amount of skin available is about 5 × 2·5 cm., but if necessary both post-auricular grooves may be used.

Excision of the malignant lesion followed by grafting the resulting skin defect is by choice carried out under local analgesia after infiltration of the local lesion and the donor post-auricular groove with 2% lignocaine and 1 in 350,000 adrenaline. To take the graft, the ear is held forward and an oval-shaped piece of skin of the size required is excised and centred over the post-auricular groove. A little allowance for shrinkage should be made, but it need only be slight. The graft must be handled gently, being held with Gillies' skin hooks as it is elevated and severed with a knife from the areolar tissue beneath. Preparation of the graft is completed by laying it on a board, or over the finger, and scraping its under-surface clean with a knife. The graft is sutured accurately, and a firm dressing of flavine and paraffin in wool pledgets applied, or a stent mould if the underlying structures are soft. The donor area is sutured.

A Wolfe graft, like other free skin grafts, is nourished by osmosis from the tissue fluid upon which it lies until such time as the ingrowing capillaries from the underlying granulation tissue have vascularized the graft, a process well under way in seven to ten days. Since a full-thickness graft is a thick tissue, particular care must be taken to prevent any unnecessary barrier between the epidermal cells and the nutrient tissue fluid, e.g. adherent areolar tissue, blood clot, and serum. Asepsis is strict and movement of the graft must be prevented to safeguard the ingrowing capillaries from injury. Even with great care a Wolfe graft occasionally exhibits surface necrosis. In such cases, however, the basal layers of the epidermis are usually well established and when the surface crust separates a well-taken graft is revealed.

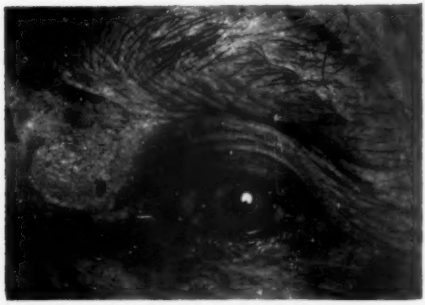
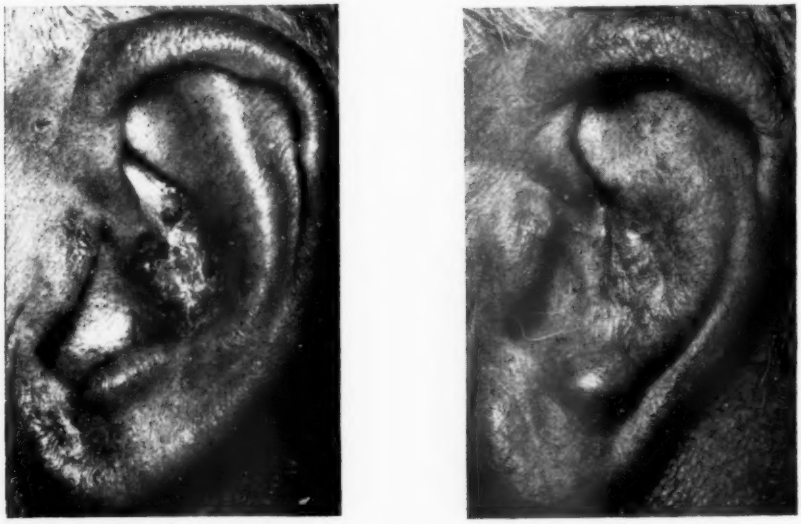


FIG. 1.—Appearance after operation and use of post-auricular Wolfe graft for a rodent ulcer above inner canthus recurrent after X-ray therapy.

Slides were shown to illustrate the use of free post-auricular full-thickness skin grafts in cases of neoplastic ulceration (chiefly rodent ulcers) around the eyelids (Fig. 1), nose, and ear (Figs. 2A and B).



A B

FIG. 2.—A, Rodent ulcer of ear. B, After excision and grafting with post-auricular Wolfe graft.

After taking a large post-auricular Wolfe graft the patient may be a little apprehensive about the resultant position of the donor ear. Initially the ear does lie closer to the head, but it is remarkable how quickly it seems to correct itself and within a month or two it is difficult to tell which ear has been used.

Wolfe grafting is often regarded as an unsatisfactory procedure, but the simple method described is appreciated by both surgeon and patient. At the time of Wolfe's death it was remarked in his obituary that he had introduced an extremely valuable modification of skin grafting which was practised abroad much more often than in this country. With the care and proper attention to detail which the operation demands, the results are very satisfying, and we can endorse Dr. Wolfe's words that "it is an operation worthy of proper appreciation" (Wolfe, 1884).

I am indebted to Miss J. Hunt of the Royal Marsden Hospital and Mr. N. K. Harrison of St. Bartholomew's Hospital, for the photographs.

REFERENCES

BLAIR, V. P. (1932) *J. Amer. med. Ass.*, **99**, 2171.
HUNT, H. L. (1926) Plastic Surgery of the Head, Face and Neck. Philadelphia; p. 175.
LAWSON, G. (1870) *Trans. clin. Soc. Lond.*, **4**, 49.
WHEELER, J. M. (1936) *Sth. med. J., Birmingham, Ala.*, **29**, 377.
WOLFE, J. R. (1875) *Brit. med. J.*, ii, 360.
—— (1884) Clinical Demonstration on Ophthalmic Subjects. London; p. 16.

# Persistent Varicose Veins with Special Reference to the Varicose Tributaries of the Superficial Femoral and Popliteal Veins

By HAROLD DODD, Ch.M., F.R.C.S.

*London*

UNTIL 1954 I regarded varicose veins and ulcers of the leg as clinical entities in themselves, but my horizon was widened when Cockett used the phrase, "the venous disorders of the lower limb", and pointed out that varicose veins, painful legs, swelling, ulceration and eczema are the effects of high pressure in the superficial veins as a result of regurgitation from the deep veins through incompetent perforating veins. Thus the problem of varicose veins and ulceration resolves itself into finding and stopping the leaks between the deep and superficial veins.

Until 1950, three sites of leak were generally recognized; the long sapheno-femoral junction, the short sapheno-popliteal junction, and the ankle perforating veins. In 1951 Dow, in his venographic studies, described a defective calf vein passing obliquely upwards to the popliteal vein and a thigh communicating vein joining the superficial femoral vein. Cockett mentioned large gastrocnemial veins in 1953. Gullmo's (1956) venograms showed varicose tributaries of the popliteal and femoral veins. Although aware that these popliteal and femoral tributaries could be varicose I hope not to meet them, but the persistence of varicose veins after apparently efficient operations drew my attention to their importance. Up to date, I think that the incidence of varicose popliteal and femoral tributaries is about equal, although I have done more operations on the popliteal vein through longer awareness.

*The Varicose Tributaries of the Popliteal Vein*

In 92 complete operative dissections of the popliteal vein the following have been found:

(*a*) *The short saphenous vein.*—As Kosinski pointed out in 1926, the termination of the short saphenous vein is variable. It may end in the popliteal space, high in the thigh, or low in the calf.

*Popliteal ending.*—It ended in the upper part of the popliteal space sixty-seven times—75%, and at the level of the knee-joint five times, making 80% ending in the popliteal space; Kosinski found 67%.

*High, or thigh ending.*—The short saphenous vein passed through the popliteal space and joined veins in the hamstrings eight times, and the long saphenous once; this equals 10%; Kosinski's was 26%.

*Calf, or low ending.*—The short saphenous vein ended in the calf five times (6%), including one joining the long saphenous vein below the knee.

In the 92 operations, the short saphenous was normal in 29, and varicose in 63, and of these it was the only varicose vessel in the popliteal space in 10, i.e. there were other varicose tributaries of the popliteal vein in 53 patients.

(*b*) *The gastrocnemial veins.*—The gastrocnemial veins arise from the inner and outer heads of the muscle. Normally each head gives off two large veins which join the popliteal vein separately at the level of the knee-joint, but they vary as follows:

(1) The veins from one or other head may join the last inch of the short saphenous vein. This was seen seventeen times from each head.

(2) Fairly often one or the other gastrocnemial vein joins the popliteal vein at the same point as the short saphenous vein, helping to form a venous web here.

(3) The veins from each head may join to form a common trunk and either pass into the popliteal vein immediately, or run to the adductor opening before joining. It looks like a double popliteal vein. These variations have each occurred twice.

The vein from the medial head of gastrocnemius is the more often varicose, this having been found fifty-one times, and varicosity of the vein from the lateral head twenty-two times.

(*c*) *Other varicose veins.*—Indirect varicose tributaries of the popliteal vein are veins which penetrate the popliteal fascia and join either the short saphenous vein towards its end, or one of the gastrocnemial veins. Such a vessel was found twenty-one times.

Veins from semimembranosus, semitendinosus and biceps are rare, but they have been seen to be varicose four times.

(*d*) ***Changes in the popliteal vein.***—The popliteal vein may be obviously inefficient as shown by its bulbous and varicose appearance. It may empty and fill with respiration and be thin-walled. Once it was partly thrombosed, whilst it has been the seat of a sacculated varix the size of a walnut. Occasionally the posterior tibial venæ comites persist into the upper popliteal space.

(*e*) ***The calf communicating vein.***—The calf communicating vein passes from the centre of the calf obliquely through the divisions of gastrocnemius to the popliteal vein at the level of the knee-joint. It has been varicose five times.

(*f*) ***The tibial communicating vein.***—This passes from the anterior vein of the leg through the deep fascia at the upper third of the tibia into the inner head of gastrocnemius, and so to the popliteal vein. This has been varicose five times.

To sum up, in 92 operations on the popliteal space, the short saphenous vein has been varicose sixty-three times and other tributaries eighty-two times; therefore I think that they must be looked for.

*Diagnosis*

Because these varicose tributaries give symptoms and signs similar to short saphenous varicosity I have formed the habit of calling them pseudo-short saphenous veins. As pseudo-short saphenous veins complicated varicosity of the short saphenous vein in 87% of this series, the signs of short saphenous varicosity are usually present. Pseudo-short saphenous veins are suggested by varicose veins about the leg, calf and popliteal space without the straight trunk of the short saphenous vein being palpable or visible.

The most valuable sign of pseudo-short saphenous varices is to palpate the popliteal space from in front whilst the knee is slightly flexed, as in standing-at-ease. A globular varix may be palpable, possibly with lateral extensions to one or other side of the mid-line. This is often the distended tortuous gastrocnemial vein which at operation may not be visible until the two heads of the muscle are separated.

Isolated varices may be seen entering the popliteal space through one of the grooves behind the knee.

*Treatment*

I now explore the popliteal vein throughout its course in all cases of short saphenous varicosity. Two incisions are available—an S-shaped and a curved. The S-shaped gives perfect exposure and good healing but is a little tedious to sew up. An incision down the centre of the popliteal space is unwise because a painful, keloid, eczematous or ulcerated scar may follow. Since June 1957 I have used a slightly curved incision about seven inches long centred at the crease of the knee-joint. The upper half is in the inner of the two grooves behind the knee, and the lower part curves gently away to the mid-line of the calf. This has healed well.

Incisions are deepened through the fat and deep fascia and the flaps reflected as necessary until the popliteal space is visible. The short saphenous vein is quickly apparent as it lies under the deep fascia in the mid-line. It is cleared and a constant tributary from the thigh is divided. In 21 out of 90 patients it was also joined by a varicose tributary which had perforated the popliteal fascia and drained varices from the thigh or leg. The sapheno-popliteal junction, usually in the upper part of the space, is sought. It entails dividing the considerable popliteal fat until the medial popliteal nerve is seen as it lies over the popliteal vein. The sapheno-popliteal union is cleared above and below. It is not often that the short saphenous and popliteal veins are alone. Frequently a large varicose trunk from either head of gastrocnemius joins here, and also several other fragile veins. It can be appropriately described as a venous web, and gross hæmorrhage may arise from it.

When the short saphenous vein passes through the popliteal space with no connexion with the popliteal vein it is followed up as high as possible and divided.

Having defined the short saphenous vein and sapheno-popliteal union, the popliteal vein is traced to the lower popliteal space. It is surrounded by the medial popliteal nerve, its sural divisions and branches of the popliteal artery. Under these are the tributaries from gastrocnemius which when varicose may be awe-inspiring. Figs. 1, 2, 3 and 4 were drawn from cases of these pseudo-short saphenous veins. The incompetent veins are divided. After this, the varicose short saphenous trunk is stripped to the ankle.

*Varicose Tributaries of the Superficial Femoral Vein*

The importance of the varicose tributaries of the superficial femoral vein passing into Hunter's canal was impressed upon me by the persistence of varices after efficient operation on the long saphenous vein. In the early cases of incompetent veins passing into Hunter's canal an incision was made over the suspected vessel to the deep fascia and the vein sought for. This was occasionally unsuccessful and tedious. Later the inner border of sartorius was exposed; this was an improvement and it led to the present practice of seeing the femoral

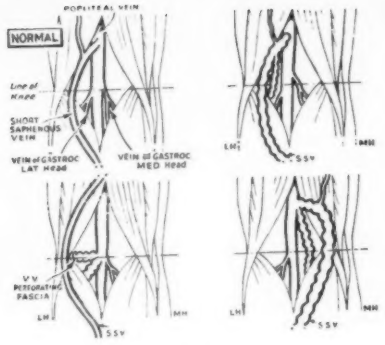



FIG. 1.

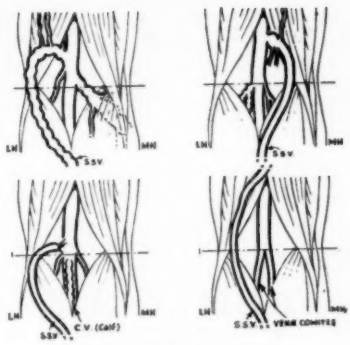



FIG. 2.

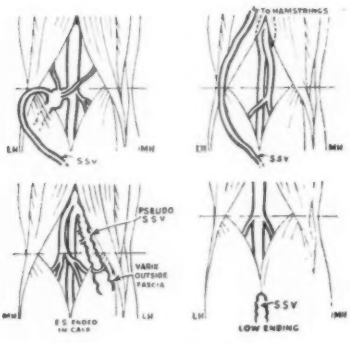



FIG. 3.

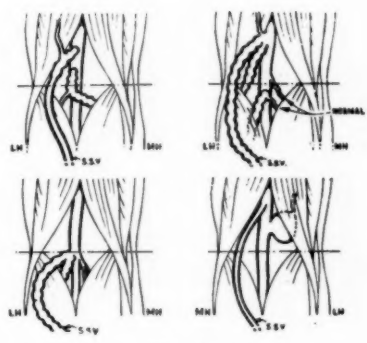



FIG. 4.

FIGS. 1–4.—Diagrams of operations on the popliteal vein and its tributaries. They are converted to the left side for purposes of comparison.

vessels in Hunter's canal, so that the varicose veins can be tied flush on the parent vein as is done for the long and short saphenous veins. This operation has revealed three to four constant small arteries accompanied by venæ comites running medially from the superficial femoral vessels, to the muscles and fat. They have been found in 30 consecutive dissections of Hunter's canal. In 6 patients a fourth vessel passed through sartorius to the fat. Any of these small veins may become impressively varicose, at times as large as the long saphenous vein. Accurate notes of the varicose findings grew slowly. They are complete in the last 20 operations, in which 10 varicosities were found involving one vessel, and 10 involving two.

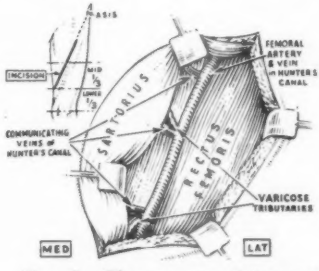



FIG. 5.—The average anatomy of the veins passing into the superficial femoral vein, two are depicted varicose. The inset shows the incision for their exposure.

*Position of the Varicose Veins*

*The lowest vein* in Hunter's canal was varicose fifteen times. These veins either passed inwards or downwards, if downwards they are the descending geniculate vessels (Fig. 5). I have found it is essential to expose the lower end of Hunter's canal where the femoral vessels pass backwards through the adductor opening. *The middle vein* was defective and enlarged on ten occasions, whilst the upper was affected three times.

Venograms indicate that these communicating veins vary in position.

*Clinical Presentation*

Patients with incompetence of Hunter's canal communicating veins—CV(H)—presen either with primary or persistent varicosities. Unlike the varicose tributaries of the popliteal vein, the diagnosis of Hunter's canal veins is straightforward by the tourniquet test. The veins are emptied, tourniquets are applied, one round the groin and the other at the lower third of the thigh, i.e. at the distal end of Hunter's canal. When the patient stands, if the veins remain empty then the short saphenous and ankle communicating veins are efficient; if they fill, appropriate tests for these veins are made. Varicosity of the short saphenous vein is occasionally present with that of the long saphenous vein and Hunter's canal veins, and its state must be determined. If it is varicose then it is kept empty by digital pressure on the centre of the popliteal space while the Hunter's canal veins are assessed. When the lower thigh tourniquet is removed the veins are watched for twenty seconds. If they fill with an appreciable degree of tension then Hunter's canal communicating veins are incompetent (Fig. 6). The filling is accentuated by asking the patient to stand on the toes twice. The diagnosis of the state of the communicating vein of Hunter's canal is essential not only for cure of the varicosities, but because their treatment requires a considerable incision across the thigh which has cosmetic considerations. I must admit to having occasionally diagnosed them but not found them; I have just undertaken my first persistent case this morning, because the first incision had not been low enough to expose the adductor opening.



FIG. 6.—The tourniquet diagnosis of a CV(H). Note the healed ulcer and pigmentation associated with it. This patient has an incompetent long saphenous vein also.

*The Treatment of Hunter's Canal Communicating Veins*

The principle is to expose Hunter's canal fully and to see the veins as they terminate in the superficial femoral vein. The incision occupies almost the lower half of the line joining the anterior superior iliac spine to the adductor tubercle of the femur, as for the classical exposure of the superficial femoral artery (Fig. 5). The skin, fat and deep fascia are divided and it leads to the outer border of sartorius. This muscle is elevated for the length of the wound until its inner border is seen. The three small arteries and their venæ comites run inwards from the femoral vessels. They arise at the upper, middle and lower parts of the canal. One or more of the veins is usually striking in its varicosity and is divided flush on the femoral vein.

## CONCLUSIONS

(1) In my experience enough varicose veins have persisted after efficient operations on the long and short saphenous veins to compel me to recognize varicose tributaries joining the superficial femoral vein and the popliteal vein.

(2) As varicose tributaries of the popliteal vein (other than the short saphenous vein) were present in 82 out of 92 cases of exploration of the popliteal vein, I expose this vessel in all cases of apparent short saphenous varicosity. I say "apparent", because a distended vein felt in the popliteal space and considered to be a varicose short saphenous vein has proved to be a gastrocnemial vein on 29 occasions.

(3) The diagnosis of incompetent veins passing into Hunter's canal into the superficial femoral vein is straightforward; I find that they complicate one in four or five cases of long saphenous varicosity. They were associated with ulceration and eczema of the ankle in 35% and 50% respectively.

## REFERENCES

COCKETT, F. B. (1953) M.S. Thesis. London.
DOW, J. D. (1951) *J. Fac. Radiol., Lond.*, **2**, 180.
GULLMO, A. (1956) *Acta radiol., Stockh.*, **46**, 603.
KOSINSKI, C. (1926) *J. Anat., Lond.*, **60**, 131.

Mr. PETER MARTIN showed a film on **By-pass Grafting of the Femoro-popliteal Artery for Atherosclerosis.**

# United Services Section

President—Sir CECIL WAKELEY, Bt., K.B.E., C.B., F.R.C.S.

[*June 5*, 1958]

## DISCUSSION: UNDERWATER EMERGENCIES IN THE ROYAL NAVY

**Surgeon Commander S. Miles, R.N.** (Royal Naval Medical School and Physiological Laboratory):

*Current Problems in Underwater Medicine*

It must be emphasized that underwater medicine is not a specialty remote from other fields. It is indeed basically environmental physiology and throughout its application the same techniques, the same ideas and the same physical principles are used as in any other branch of environmental research be it clinical, climatic, aero-medical or industrial. So too will achievements in underwater research contribute in some measure to progress in these other spheres. Scientific and mechanical development in recent years have produced means which enable man to exist actively and travel in environments which normally would not support life. In aviation, space travel and even under the sea, the range of activity is restricted by the physical limits of human tolerance rather than the capabilities of the vehicles in which he may travel. Diving apparatus and submarines have been developed which can take man deeper and for greater lengths of time than he himself can endure. Thus it will be seen that current problems in underwater medicine demand the study of man's responses to the new environments.

In underwater medicine there are two major environments to be considered. First that of the submarine where, though the air in the vessel remains at atmospheric pressure when submerged, it cannot be refreshed from without and equipment must be carried for production of oxygen and removal of carbon dioxide and other noxious agents. The advent of the nuclear submarine with prolonged underwater cruising will greatly magnify these problems. Lieut.-Commander John H. Ebersole (1958) of the United States Navy has recently given a full account of this subject to the Society. So I will pass directly to the second environment, that of the diver.

Whether the diver be free swimming, taking his atmosphere in bottles with him or whether he be supplied from the surface in the conventional method, the air must be supplied to him at a pressure equal to that of the surrounding water. The human body submerged behaves as an incompressible fluid, its tissues taking on the equivalent pressure without deformity or conscious change. The air in the lungs is, however, compressible and therefore, for normal functioning, must be supplied at greater pressure and volume. This in turn means that both nitrogen and oxygen will dissolve in the blood and pass into the tissues in greater amounts than those to which the body is adapted. It is this need to increase pressure and flow of air which gives rise to difficulties in adaptation which may best be described under five headings: (i) changes in pressure and volume; (ii) increased air density; (iii) increased oxygen pressure; (iv) increased nitrogen pressure; (v) decompression.

*Pressure and Volume Changes*

As far as the lungs are concerned, as long as the pressure of the respiratory gas is kept the same as that of the surrounding tissues no harm will result. An excess may force air into the pleura or lung capillaries; a lower pressure may result in a "squeeze", a situation

in which a diver is crushed into his helmet by water pressure. The importance of the former will be described by a subsequent speaker, the latter is an unimportant rarity. Some idea of the extent of the volume changes may be appreciated by realizing that to descend as little as 33 feet in the sea doubles the pressure. A man who dives without apparatus with his chest in full inspiration—perhaps containing 6 litres—will be in full expiration with 1½ litres (the residual volume) if he swims down to a depth of 100 feet. Many other inconveniences, sometimes serious, may occur due to pressure changes of air in the middle ear or sinuses or gases in the alimentary tract or at the roots of carious teeth.

*Increase in Air Density*

As air pressure is increased so will its density become proportionately greater. It is found in practice that the maximum breathing capacity of a diver is halved at a depth of 100 feet. Thus resistance to breathing will be considerably increased with diving, not only the individual's personal respiratory resistance, but also that of any apparatus he might be using. A breathing set with an acceptable resistance at the surface may be quite unsuitable for use at depth. Careful attention must be paid to the effect of density when designing underwater breathing apparatus and assessing man's underwater efficiency. Many inexperienced divers have been alarmed by the increased respiratory effort required for even moderate work.

*Increased Oxygen Pressure*

When pure oxygen is breathed at atmospheric pressure certain changes occur. Because more oxygen is in solution in the blood this will be used first by the tissues so that there will be less reduction of oxyhæmoglobin. This lessens the efficiency of the blood in removing carbon dioxide from tissues. Changes in intracellular metabolism are believed to result from excess oxygen affecting enzyme systems, e.g. the inhibition of enzymes with the sulph-hydryl group and a depression of the acetylization of choline (Haugaard, 1955). Whatever the biochemistry, a significant effect in man is a considerable reduction in the cerebral blood flow—a reduction which is not met by the excess oxygen carried. This results in a lowering of the syncope threshold (Miles, 1957). In practice it is found that swimmers breathing oxygen, even at relatively shallow depths, may lose consciousness as a result of the summation of this reduced syncope threshold with other syncope-promoting factors such as anxiety, hyperventilation, increased intrapulmonary pressure, alcoholic hangover, hunger and ill-health. This is the underlying mechanism of a condition which has been called in the diving world "Shallow Water Blackout" and which has a parallel in the "aero-syncope" of aviation medicine. The term "oxygen syncope" has been suggested to describe the condition in divers and because of this risk, which is greater in inexperienced men, the Navy is developing an air-breathing set to replace the oxygen breathing sets for training and general use, restricting the use of the closed-circuit oxygen set to operational circumstances where it is essential that to limit detection no bubbles are produced.

Furthermore, if pure oxygen is breathed at pressure more than twice that of the atmosphere, e.g. at depths of 33 feet or more, convulsions may occur, the classical sign of oxygen poisoning (Donald, 1947). These convulsions are epileptiform and may be preceded in some cases when a mouthpiece is used by lip twitching. The convulsion is the manifestation of oxygen poisoning but it is reasonable to assume that before this dramatic event occurs some changes in the central nervous system must be taking place. To find out what these changes are is a major requirement for the underwater physiologist. Is oxygen syncope a mild form of oxygen poisoning and is the final convulsion due to anoxia or retention of carbon dioxide? There is perhaps a clue to this in the "oxygen paradox" where giving oxygen to an individual who is nearly unconscious with anoxia may produce temporary loss of consciousness. On the other hand oxygen syncope and oxygen convulsions may be compared with *petit mal* and *grand mal*.

If a study of partial pressures is made it will be seen that breathing air at a depth of 280 feet produces the same oxygen pressure as pure oxygen at 33 feet. Thus at this depth or deeper there would be a risk of oxygen poisoning whilst breathing air, a fact which would in itself make it dangerous to use air for diving at such depths.

Much more work is needed before the mechanism of oxygen poisoning is understood but recent work has shown a similarity between oxygen poisoning and X-irradiation in that both produce, in the tissues, oxidizing free radicals. In clinical practice high pressure oxygen is used to increase the effectiveness of irradiation in the treatment of cancer.

Oxygen also has a chronic effect. Animals breathing pure oxygen at atmospheric pressure may die in about ten days from pulmonary œdema and pneumonia, and infants breathing oxygen for prolonged periods have developed retro-lenticular degenerations.

*Increased Nitrogen Pressure*

When air under pressure is breathed, the partial pressure of its nitrogen will be correspondingly greater and when excess nitrogen diffuses into the tissues it produces a narcotic effect which at a depth of 200 feet may render an individual incapable of accurate thought and action. With training however, an experienced diver may do useful work at 300 feet. A similar condition may be produced by breathing 20% nitrous oxide at the surface. The effect of nitrogen can be shown to abolish alpha-rhythm blocking in the EEG record and to vary the threshold of fusion of a flickering light. It becomes apparent that though gross effects are rarely seen at depths less than 150 feet changes are taking place even at shallower depths. There is some evidence that even at atmospheric pressure the ambient nitrogen has some blanketing effect on the central nervous system, for its removal by breathing oxygen or oxy-helium mixtures or reducing nitrogen pressure by altitude does, in many cases, produce exhilaration and increased acuity. This is at present largely speculation but it is an interesting conception that nitrogen, far from being an inert gas may play a part in damping nervous activity. Further work is being planned on this rather unusual idea of the "nitrogen blanket". As with oxygen, the nitrogen in the air breathed will limit an experienced diver's usefulness to about 300 feet.

*Decompression*

Having established that a diver may breathe air with comparative safety down to a depth of 300 feet, this is not the end of the story. At the increased pressures both oxygen and nitrogen will dissolve in excess in the blood. The oxygen will be metabolized but the nitrogen will diffuse from the blood into the tissues. The important point is that the excess gas passes into the body through the lung alveoli during the pressure increase. If pressure is suddenly released the change will be felt throughout the tissues and if the drop in pressure is great enough bubbles will form in both blood and tissues producing what is called "decompression sickness". The symptoms of this may be rashes, itching, painful joints (bends), pulmonary irritation or cerebrospinal involvement according to the degree of bubble formation. Fat cells may be ruptured, producing lipæmia, and cases have been reported in obese men of fat emboli passing through a patent foramen ovale to lodge in the brain. Decompression sickness is by no means confined to divers. It occurs quite commonly in men working under pressure in the construction of underwater tunnels and is a well-known hazard for airmen subjected to explosive decompression. The only way in which the condition may be avoided is to ensure that the decompression is so slow that the excess nitrogen can be given off from the lungs before bubbles form. Though ideally a diver would be brought up to the surface very gradually it is convenient and effective to bring him up in steps of 10 feet allowing him to rest appropriately at the various stages.

The adverse effects of density, oxygen, nitrogen and decompression sickness which have been outlined have not prevented a diver reaching a depth of 600 feet and perhaps the most interesting way of showing how the difficulties may be overcome would be to describe how in 1956 Lieutenant G. A. M. Wookey, a naval diver, established the world's record dive to a depth of 600 feet off Norway. At this depth he was able to do useful work for five minutes. Had he been breathing air, narcosis would have rendered him unconscious. If this could be prevented oxygen poisoning could still occur and even if this too could be prevented the increased air density would make breathing very difficult and work impossible. The dangers of long decompression still remained. What then was done?

Briefly, the diver descended to 40 feet breathing air. Here the air was replaced by a mixture of 8% oxygen in helium. At this depth it will be found that 8% oxygen exerts the same partial pressure as 21% oxygen (e.g. air) at the surface. Also 8% oxygen at 600 feet has a partial pressure less than the threshold for oxygen poisoning. Thus the risk of oxygen poisoning is removed. At the same time helium has not the narcotic properties of nitrogen and can be breathed with safety at this depth. Finally because the atomic weight of helium is much less than that of nitrogen the resultant mixture has, at a depth of 600 feet, only half the density of air, and thus offers a resistance to breathing which is acceptable. With this mixture Lieutenant Wookey was able to reach the bottom in about five minutes and complete his allotted task chosen to simulate the work a diver might do to secure a rescue bell to a sunken submarine.

Although this simple breathing mixture took the diver safely to the bottom the problem of decompression still remained, for helium would dissolve in blood and tissues in a manner similar to nitrogen. This had been calculated to require about seven and a half hours of decompression—a time which, in cold Norwegian waters, was more than any man could tolerate. The pressure changes in water are such that as the diver gets deeper, a much greater distance up or down can be undertaken than when he is nearer the surface for the same

relative change in pressure. For this reason an ascending diver can come about two-thirds of the depth before stopping and thereafter, coming up in 10-foot stages, he must have increasingly longer stops.

It was therefore possible to bring him up to 200 feet in a very short time. At this depth he was met by a submersible decompression chamber, a form of diving bell, filled with air at a pressure equivalent to the depth. This the diver could enter to find a companion waiting to remove his helmet give him a hot drink and encouragement. Maintaining the pressure within equivalent to a depth of 200 feet, the chamber was hoisted in-board the attendant vessel and the tedious process of decompression completed in security and with a tolerable degree of comfort.

It is likely to be a long time before a further attempt on this record is made as research is being directed from deep diving to the self-contained, free-swimming diver who must take his atmosphere with him in bottles. He has a much greater mobility and freedom and although he cannot at present do much below 200 feet this is sufficient for most general needs. Physiologically the problem will be very much the same but there is one striking difference. The standard diver is fully controlled both in ascent and descent by a team of attendants on the surface. The free diver on the other hand, as the depth and endurance of his breathing apparatus increase, is himself responsible for controlling his depth, timing his duration and working out his decompression. The vital question is whether he can do this safely under the influence of even minor degrees of nitrogen narcosis. This we have yet to find out and for this reason we must learn more about nitrogen narcosis and how it may be avoided or controlled.

Time does not allow mention of the many other interesting aspects of underwater medicine. My two colleagues will be presenting subjects of exceptional practical application about which they are both well qualified to speak. Even so, there is no time to refer to other areas of interest, problems of apparatus design, underwater propulsion, the effects of the blast of underwater explosions on men under water, problems of vision, sound and detection. There is also much for us to learn from the behaviour and anatomy of seals and whales and if this summer the much-advertised television search for the Loch Ness monster is successful, who knows what secrets may be revealed!

REFERENCES

DONALD, K. (1947) *Brit. med. J.*, i, 667.
EBERSOLE, J. H. (1958) *Proc. R. Soc. Med.*, **51**, 63.
HAUGAARD, N. (1955) Effect of high oxygen tensions on enzymes, *U.S. Nat. Res. Coun. Publ.*, p. 377.
MILES, S. (1957) Oxygen syncope. Med. Res. Coun. Report R.N.P. 57/880.

**Surgeon Lieutenant R. J. W. Lambert, R.N.** (H.M.S. *Dolphin*):

*Submarine Escape*

During the last half-century, many methods have been devised, by which the crew can escape from a submarine, should it fail to surface. The requirements of any method of submarine escape are firstly, that it shall be simple enough to be understood by, and gain the confidence of, the least intelligent member of the ship's company; secondly, that it shall be independent of help from surface vessels or other outside aid, and, lastly, that the apparatus involved shall not be so bulky as to affect adversely the essentially offensive role of the submarine as a weapon or to render it more vulnerable to enemy action, or the normal hazards of its underwater environment.

Methods which have failed to satisfy these criteria include various types of salvage, and the "rescue bell". The latter is a diving chamber which is lowered on to the deck of the sunken submarine from a vessel moored on the surface so as to make a watertight seal over one of the hatches, enabling the submarine crew to be transferred in batches to the surface, without their being subjected to increased pressure. Although it was dramatically successful in rescuing the crew of the United States Submarine *Squalus* in May 1939, the odds against a vessel carrying this bell being in the vicinity of the sunken submarine and being able to moor with sufficient accuracy in the face of possibly adverse surface conditions quickly enough to rescue the crew before they succumb to the atmospheric conditions in their submarine, are so great, that it has recently been dropped altogether by the Admiralty as a practical method of saving life from sunken submarines.

This has confined the subject of escape to methods which can be operated solely from within the submarine and these all have the disadvantage of subjecting the escapees to

increases of pressure and the physiological hazards that go with them, during their escape, in addition to the obvious psychological stress of such a situation. The existing methods are "compartment escape" as the primary one, and "tower" or "chamber escape" as the secondary method. Compartment escape consists of a compartment at either end of the submarine, equipped with hatches from the margins of which a length of twill trunking can be lowered to within a few feet of the deck. The compartment is then sealed off from the other parts of the submarine by watertight doors, and flooded. As the water rises the air in the compartment is compressed, until the point is reached at which the pressure within is equal to that outside the hatch and this can then be opened. The trunking fills with water, at the same time preventing the residual pocket of air from escaping. The crew stand with their heads above the water, and in turn duck inside the trunking and climb out through the hatch.

In tower escape, the survivors leave in pairs by means of a specially fitted conning tower, or gun tower, or a specially constructed chamber built into the hull of the submarine, which is flooded up until the pressure is equalized. The pocket of air is then vented through a valve into the sea and the hatch opened. After each pair has left, the hatch can be closed and the chamber drained by remote control from within the submarine, ready for the next escape.

If the submarine has been submerged for any length of time before the escape commences, the atmosphere within it may contain up to about 5% carbon dioxide, so that during flooding, as the pressure rises, the partial pressure of $CO_2$ may well rise to toxic levels. To solve this, in the past oxygen was breathed during the flooding and the ascent. The apparatus from which this was breathed—in the case of the Royal Navy the Davis Submarine Escape Apparatus, in the American Navy the Momsen Lung, in the German Navy the Draeger Lung—served both as an underwater breathing set, and as a source of buoyancy to bring the escapee to the surface. During the 1939–1945 War the hazards of acute oxygen poisoning became increasingly recognized, and in April 1946 an Admiralty Committee, under the chairmanship of Rear-Admiral P. Ruck-Keene, C.B.E., D.S.O., was set up to consider existing methods of escape and to make recommendations for the future. This Committee found that a surprising number of men escaping from submarines of all nationalities during and before the War, had reached the surface without any kind of breathing apparatus. It was also found that many men who had breathing sets, used them incorrectly, due to the stress of the situation, and lost their lives, and that many more who used them correctly succumbed to oxygen poisoning. As a result of this Committee's recommendations the method now known as "free ascent", or in the United States Navy "buoyant ascent", ultimately came to be adopted.

*Free Ascent*

This method depends essentially upon a man filling his lungs at a pressure equivalent to the depth of water, before leaving the submarine, and exhaling continuously throughout his ascent, as the pressure on his chest decreases and his lungs therefore expand. Since the partial pressure of oxygen in his original lungful of air is high, this will be adequate to fulfil his needs provided his ascent is not unduly prolonged. Similarly, provided his ascent is not unduly prolonged he will eliminate sufficient $CO_2$ in his exhaled air to keep his alveolar partial pressure of $CO_2$ within tolerable limits. As a result of experiments carried out in the Royal Naval Physiological Laboratory, reported by Taylor (1953), a suitable rate of ascent was found to be about 5–7 feet per second. At this rate it can be shown that, for an average man making an ascent, rather more than two-thirds of the $CO_2$ he produces is eliminated in his exhaled air, so that the increase in his alveolar $CO_2$ partial pressure is well within tolerable limits from depths as great as 300 feet. This rate is achieved by the escapee wearing a 14-litre capacity bag as a stole over his submarine escape immersion suit, filling it first at a pressure equivalent to his depth. A valve on it that lifts at ½ pound per square inch keeps its volume, and therefore his rate of ascent, fairly constant on the way up. With the abolition of oxygen breathing sets the problem of $CO_2$ partial pressure during the flooding up stage has been solved by the construction within the escape compartments of what is known as the "Built-in Breathing System". By means of this, air, or any suitable mixture of oxygen and nitrogen is delivered through a special system of valves so as to reach the escapee at the ambient pressure throughout flooding up. At present the gas supplied in this is a 40% : 60% oxygen : nitrogen mixture. The reason for this is to reduce the risk of nitrogen narcosis interfering with a man's drill before he leaves the submarine, and that of a subsequent bend occurring after he reaches the surface, by reducing the nitrogen content, so far as this is possible without the percentage of oxygen being so high as to produce a serious risk of oxygen convulsions. Breathing a 40% : 60% mixture at 2 8 feet (10 atmospheres absolute) is equivalent, from the point of view of oxygen poisoning, to breathing pure oxygen at 99 feet (4 atmospheres absolute). It is true that at this depth

if the mixture is breathed for more than a few minutes the oxygen content does become a hazard, but at 298 feet so many other factors are present to lessen the chances of a successful escape, that the added risk of oxygen poisoning is a relatively small one, and while a change to compressed air would virtually abolish all risk of oxygen poisoning, it would slightly increase the hazard of nitrogen narcosis and of bends at the lesser depths where there is a much greater chance of a high percentage of lives being saved.

*Pulmonary Barotrauma*

The main risk of the ascent to the surface is that of pulmonary barotrauma, which can sometimes result in traumatic air embolism. The former is caused by an increase in the intrapulmonary pressure throughout, or in a part of the lungs, which stretches and tears the alveoli, forcing air into the interstitial tissues, and in more severe cases, rupturing pulmonary vessels so that air is sucked into them and thus enters the systemic circulation. This condition was first described by Adams and Pollak (1932) following a death occurring in American submarine escape training. It is not confined to free ascent, and, indeed, the death they reported occurred in the case of a man wearing the Momsen Lung, but it is probably a more prominent risk in free ascent than in ascents with breathing sets or in diving operations generally.

Since the adoption of "Free Ascent with Buoyancy" by the Royal Navy in 1954, practical training for all submariners has been carried out in the Submarine Escape Training Tank at H.M.S. *Dolphin*. Up to date, approximately 6,900 men have passed through this course, and as the practical part of it consists of one free ascent without buoyancy from 15 feet, and two ascents from 30 feet, one from 60 feet and one from 100 feet, all with buoyancy, over 34,000 escapes have been made. Of this number a tiny, but significant, proportion of casualties has occurred. The number to date is 12, an incidence of only slightly more than 1 in 3,000. Of these, 10 have had symptoms primarily of cerebral air embolism; the other 2 have shown a clinical picture of widespread damage in the thorax without associated neurological symptoms. In no case has the condition been fatal. However, the organization of the Submarine Escape Training Tank makes provision for these cases, and has an efficient drill for rapid recompression.

The manifestations of air embolism have been varied, as would be expected, including cases complaining of vertigo with tingling in one or more limbs, both spastic and flaccid pareses, transient interference with vision—in one case the loss of the left field, in another, central scotoma, and in two cases repeated epileptiform convulsions. In the treatment of all these cases it is essential to recompress with the minimum delay and since recompression has usually quickly abolished all symptoms it has generally been impossible to get localizing signs for the lesion. In at least 4 of these cases electro-encephalography has afterwards confirmed the presence of some central nervous focus but usually this could not be done until twenty hours or more after the accident, since therapeutic recompression takes at least nineteen hours. Of the 2 cases without signs of air embolism, both had severe mediastinal emphysema spreading up into the neck and 1 of them in addition had a bilateral pneumothorax, a closed one on the left and a tension pneumothorax on the right. In only about half of these cases did the subject remember pain or a feeling of over-inflation in his chest on his way up, and although in several of them the ascent was noticed to be a bad one, in so far as the man was seen to breathe out either intermittently or rather less than average, in none of them was the ascent markedly worse in this respect than in very many others who arrive on the surface without symptoms. Time does not allow me to go into the many interesting clinical points arising in these cases, and in any case there is very much more to be learnt about the various sites of, and mode of action of, air emboli within the brain, but obviously one of the first questions is whether the damage occurs in a completely healthy pair of lungs or whether, in fact, there was some predisposing pulmonary anomaly. In favour of the latter is the fact that more than one of these men ascending from 100 feet can recollect a sensation of running out of air somewhere around the 60-foot level. If they were in fact down to their residual air at this point it is obvious that the total expansion between there and the surface would be well within physiological limits. In addition, before starting to make any ascent each man is held by the tank instructors until it has been ascertained that he is breathing out freely, so that in fact he has blown out an appreciable volume of air before he starts to rise. In view of this, and the fact that all those who have subsequently become casualties have been seen to be blowing out at least most of the way up, it would seem to suggest that some predisposing cause in the lungs must be responsible. These men, who are young, healthy submariners, have been clinically examined regularly, their medical histories have been gone into carefully and their chests have been recently X-rayed, before they attempt the training course, so one may exclude any gross chest pathology.

Possibilities put forward to explain the mechanism of the original damage have included:

(1) *Emphysematous bullæ* which might rupture at a lesser differential of pressure than it would take to damage the alveolus. This could explain one or two of the cases, but it is difficult to make it fit the facts of most of them.

(2) *A build-up of pressure* in one or more pockets of the lung. Here it is visualized that a partial blockage of a smaller air passage might, while allowing the pressure in the zone it supplied to equalize with the rest of the lung during the flooding or compression stage, where the increase in pressure is relatively slow, nevertheless block the escape of air sufficiently, during the rapid decompression of the ascent, to allow a pressure build-up to occur, leading to alveolar rupture.

A gross case of this was thought to have occurred with a fatal result in the United States Submarine Escape Training Tank in New London in April 1957. A trainee arrived at the surface unconscious and died a few minutes later in the recompression chamber. At the post-mortem one bronchus was found to be partially blocked by a calcareous body, which was thought to be derived from a calcified gland, and having eroded through the bronchial wall and travelled along the bronchus to a point where it blocked it, to have formed in fact a "ball valve". Both the damage to his lungs and intracranial damage due to air dissection were extensive. While this pathology must be very rare indeed, it does seem possible that some similar mechanism in a milder form could be responsible for some of the cases encountered.

(3) *Compensatory alveolar emphysema.* In a paper published in 1943, Macklin and Macklin suggested that several factors working together led to pulmonary interstitial emphysema. Firstly they suggested that if, in the past, there had been an atelectasis of one small region in the lung, too small afterwards to show on X-ray, nevertheless it might cause sufficient compensatory emphysema in its immediate environment to produce a potential weakness. Secondly, they pointed out that the pulmonary blood vessels surrounding the alveoli acted as a buttress to their walls. In a normal inspiration, as the alveoli increase in size so also does the pulmonary blood flow and so the calibre of the pulmonary blood vessels. In other words, as the walls are stretched, so the buttressing effect is increased. In abrupt decompression, however, the pulmonary blood vessel calibre is decreased if the lungs become over-inflated, due to direct pressure on the heart and great vessels by the expanded lungs and pressure on the pulmonary capillary bed, by the expanded alveoli. The combination of these two factors could again be a cause of alveolar rupture.

If one regards the alveolus as a square box with four sides surrounding its entrance and a base opposite, the four sides, or alveolar ring will be able to stretch to a greater degree than the base which will be the point of rupture. Alveolar bases are of two types: those which rest on connective tissue, for instance the blood vessel sheaths, and those where the base is a partition simply between two adjacent alveoli. In the first type, if this connective tissue is part of the perivascular sheath, following rupture the air will find its way to the hilum via this sheath and the bronchovascular rays, and so set up a mediastinal emphysema. Having started to travel in this direction other respiratory movements will produce a pumping action to keep the flow going, and may indeed result in a positive build-up of pressure in the mediastinum. In the second case a minor rupture of the base which did not tear the blood vessels would produce no symptoms, for the air would simply pass into an adjacent alveolus, and indeed it has been suggested that there are "physiological pores" connecting adjacent alveoli. A more severe rupture, however, might tear the vessels within the base and the vein being collapsed at the time of tearing would be in the perfect state to suck air in subsequently, and so produce air embolism.

These suggestions as to the cause and mechanism of pulmonary barotrauma admittedly leave many points open to criticism and very much more experimental work will be needed before it can be said with certainty how the damage does occur in these occasional submarine trainee casualties. Nevertheless, it is a subject of great interest as well as one of great practical importance, for if healthy lungs are being damaged during training, then somewhere possibly the drill is at fault and must be changed. If, however, there is some predisposing anomaly of the lungs the problem becomes one of diagnosis and personnel selection, and perhaps, with the ever-increasing diagnostic potentialities of radiography, even these anomalies may be picked up on X-ray in the future.

## REFERENCES

ADAMS, B. H., and POLLAK, I. B. (1932) *Nav. med. Bull., Wash.*, **30**, 165.

MACKLIN, C. C., and MACKLIN, M. A. A. (1943) Essays in Biology. Berkeley, Cal.

TAYLOR, H. J. (1953) Recent Research in Submarine Escape. Admiralty Report **U.P.S. 137. U.N.P. 53/778.**

**Surgeon Lieutenant Commander J. S. P. Rawlins, R.N., M.B.E.** (Royal Naval Medical School and Physiological Laboratory):

*Escape From Submerged Aircraft*

One of the hazards of operating aircraft from ships is the liability of the aircraft to take a sudden plunge into the sea, with little or no warning, from an altitude which renders escape by parachute out of the question. Fortunately, in the past, aircraft have tended to float for a considerable period which has afforded the crew a fair chance of effecting an escape. But the advent of the jet-plane has considerably reduced this tendency for the engines, being not only exceedingly heavy but basically little more than highly-specialized drain-pipes, offer little or no obstruction to the process of flooding-up, and the only structures providing temporary buoyancy are those few compartments of the wings and fuselage which are not occupied by mechanical and electrical equipment, and the pilot's cabin.

When the present generation of Naval aircraft was visualized, the situation was observed to deteriorate further, for their design necessitated taking-off and landing with the pilot's canopy locked, and their weight exceeded 15 tons—about double the weight of a London bus, and if you can visualize the problem of escaping from a London bus dropped into the sea from a height of 50 feet you will readily appreciate that aircrew were becoming a little apprehensive about the possible outcome of a ditching!

In June 1954 the matter was discussed at the Ministry of Supply and at the same time a survey was made of the lethality of recent ditching incidents. The latter revealed that 30% of aircrew involved in any form of ditching failed to escape, and there appeared to be no record of a successful escape from aircraft which had entered the water in the inverted attitude. It was concluded that a practical investigation of the problems involved in abandoning a submerged aircraft was an urgent requirement.

Subsequently various proposals for facilitating escape were put forward, ranging from the siting of explosive charges to cut away part of the fuselage enclosing the cockpit, to the provision of large flood-valves which would allow water rapidly to enter the cockpit and thus prevent the creation of a large differential pressure between the air trapped within it and the water surrounding the sinking aircraft. The Institute of Aviation Medicine favoured the use of the ejection-seat which if it could be made to function under water would carry the pilot clear of the wreckage and subsequently release him automatically from his seat harness and allow him to swim unimpeded to the surface.

It was appreciated at that stage that the problems involved in such a procedure would be as follows:

(1) The effect of the shock-wave from the ejection-gun cartridge (which contained up to 2,300 grains of cordite and was capable of catapulting a 150 lb. man and an 80 lb. seat 80 feet into the air).

(2) The effect of the drag engendered by driving seat and man through the water at higher accelerations and higher velocities than had ever voluntarily been experienced before.

(3) The effect on the lungs of the rapid expansion of their contained air when a man was shot from a greater to a lesser depth.

Various acknowledged authorities were consulted and at a meeting on October 12, 1954, it was concluded that escape by this method was not feasible. On the following morning news was received that Lieutenant Bruce McFarlane, Royal Navy, had successfully escaped from a Wyvern aircraft by ejecting himself underwater.

It was almost two years before an opportunity arose of starting practical work on the project. Tests had been ordered on the underwater-jettisoning characteristics of the pilot's and observer's canopies in Vixen aircraft, and it was arranged to carry out some live escapes during this trial. Part of the fuselage of the aircraft, containing both pilot's and observer's compartments, was mounted in a steel frame with 7,000 lb. of ballast and so arranged that it could be lowered into a 40-foot-deep tank. A number of preliminary runs were made to ascertain whether the build-up of pressure would be so great as to cause the walls of the cockpit to implode, and when it was apparent that this was not going to happen a team comprising a doctor and three divers took it in turns to descend in the fuselage to various depths and try to jettison the canopies and escape. All wore conventional frogman-type gear and usually one occupied each compartment while the other pair remained in the water as a stand-by team to extricate the subjects should the fuselage collapse or the in-rush of water when the canopies were jettisoned dislodge their breathing apparatus. Tests were made in both the normal and inverted attitudes.

The impression created by the first test was unforgettable. As the fuselage sank water

poured into the cockpit through heating and pressurization-ducts and various other orifices. When the cockpit was about half full the canopy-jettison system was operated. Explosive jacks blew off the canopy with a loud bang and water poured in from all angles, buffeting the subject's head to and fro and threatening to knock off his face-piece. Suddenly it was all over and there was complete silence and the subject was able to release his harness and float up to the surface.

The conclusions drawn from these trials were that the chances of escape from Vixen aircraft submerged in the normal attitude were good provided that the rate of flooding-up of the cockpit was sufficiently large in relation to the rate-of-sink to prevent the canopy being held in place by the creation of a large cockpit/water differential pressure; but the chances of escape from an aircraft in the inverted attitude, where the pilot's head would be submerged first during the process of flooding-up, were frankly remote. Accordingly investigation of the possibility of using the ejection-seat underwater was strongly recommended.

The next phase was begun in February of the following year by firing a seat with a dummy pilot from an iron frame bolted to the floor of a tank at the Royal Aircraft Establishment, Farnborough. Records were taken of the acceleration of the seat and of the velocities achieved, and the parameters of the shock wave generated by the explosion of the ejection-cartridge were determined from recordings obtained by crystal pressure gauges located 18 inches from the point of separation of the two parts of the ejection-gun and at the wall of the tank.

The maximum figures thus obtained with various types of ejection-gun were as follows:

(1) Velocity: 34 ft./sec.
(2) Acceleration: 5 g.
(3) Blast pressure: 26 p.s.i.
(4) Height of rise of seat: 17 ft.

The question of velocity was tackled first. A metal trapeze was constructed which was attached by a wire to a streamlined float. A second wire connected this via a single sheave to a 2·4 litre Jaguar car. The subject clung to the trapeze, which rested on the bottom of a 30-foot-deep lake and having made a maximum expiration to lessen the dangers of lung damage during his ride toward the surface signalled that he was ready to go. The Jaguar then accelerated along the lakeside from a racing start, pulling the trapeze up from the bottom at a shallow angle and then horizontally at a depth of 10 feet across the lake. A maximum speed of 44 ft./sec. was achieved in this manner with no damage to the subject other than some residual stiffness.

On the effects of high accelerations under water no information was forthcoming. It was suggested that acceleration—as opposed to velocity—might have a profound effect upon the drag because it was known that in order to initiate movement in an immersed body much energy was required to start the water flowing, but all the experience of the hydro-dynamicists related to the behaviour of spherical or ellipsoidal bodies and no forecast could be made which would apply to a pilot and ejection-seat.

It was decided therefore to tackle the remaining questions together by carrying out actual ejections with live subjects but with reduced charges.

The first of these, with 350 grains of cordite, took place in the tank at Farnborough during May. The subject, wearing breathing apparatus, was strapped into the seat at the bottom of the tank. A second diver stood by as the tank was filled up. As before, the subject made a maximum expiration and then signalled that he was ready. Five seconds later the seat was fired by remote control from the surface. The test, although a somewhat exhilarating experience, was entirely successful.

A few days later a second shot with 750 grains of cordite was made and this time both subject and attendant were considerably shaken by the force of the explosion which was enhanced by reflected waves from the walls of the tank.

It was decided that the possibility of injury with the next (1,500 grains) charge could not be excluded and the project was therefore transferred to another tank which was much larger and in which full photographic records could be obtained by means of high-speed cameras.

Further tests with dummies had to be carried out to determine the characteristics of the shock-wave in the larger tank and to check the integrity of the tank walls, for one side was entirely constructed of glass and the pressure on the lowest panes was of the order of 10,000 lb.—comparable to the thrust of a modern jet-engine at full throttle, and the effect of a broken window on personnel both inside and outside the tank can be imagined.

In point of fact in each test one person only was allowed within the danger area outside the window—the officer responsible for directing the operation on whom the safety of the divers depended; all the cameras and recording equipment were operated by remote control the operators being linked to the controlling officer by means of an inter-communication system. A foolproof system of controlling the divers and technical sections was devised and practised with due allowance for misfires and other eventualities, and in the absence of an emergency recompression chamber all subjects were required to breathe out and to be seen to breathe out before the signal to fire was given.

By the end of July, five months after the first dummy tests at Farnborough, a "live" shot with the full ejection-seat-charge had been successfully completed and since then a total of 13 live shots with four subjects has been accomplished. In addition dummies have been fired through the Perspex canopies of submerged fuselages to assess the risk of damage from striking the canopy, and the possibility of eliminating the shortcomings of the present ejection system by modifying the gun for use with compressed-air has been investigated.

The conclusions drawn from these experiments are as follows:

(1) When the canopy is open or off, escape from a submerged aircraft can best be made by climbing out, inflating the survival waistcoat and ascending to the surface, breathing-out all the way.

(2) When the canopy is locked in position it is better to employ the ejection-seat, firing it through the canopy if the latter is of frangible plastic, or if it is reinforced waiting for the cockpit to flood-up before jettisoning the canopy and then firing the seat.

(3) In all cases it is necessary to safeguard the lungs against the change in pressure by breathing-out prior to firing, and also on the way to the surface after the seat-harness has been automatically released.

Recommendations have been put forward for modification of all ejection-guns, to ensure their proper functioning under water, and the need for further investigation into the development of an auxiliary system for operating the ejection seat in aircraft with infrangible canopies has been stressed.

Fleet Orders, based on these conclusions and recommendations, are being promulgated and it is hoped to establish a training programme in the near future.

It remains to be seen whether the present mortality of 30% from ditching accidents can be reduced.

# Section of Anæsthetics

President—B. L. S. MURTAGH, M.B., F.F.A.R.C.S.

[*April* 11, 1958]

MEETING TO COMMEMORATE THE CENTENARY OF THE DEATH OF JOHN SNOW

## John Snow's London Associations

By GEORGE EDWARDS, L.R.C.P., M.R.C.S.
*London*

THE year 1958 is the centenary of John Snow's death and we pay tribute to the memory of one who has rightly been called the first specialist anæsthetist. He died at the age of 45, a short life by our standards. Nevertheless, in his limited time, John Snow proved himself to have been an anæsthetist without equal, and also a brilliant epidemiologist. He carried out an investigation into the causation of a cholera epidemic which was not only an invaluable contribution towards the control of that scourge but was also a classical example of how such researches should be made [1, 2].

There are many ways in which the task of recounting Snow's great qualities could be approached and I propose first to consider the various societies and establishments to which Snow belonged and then to enumerate the memorials which remain to his honour.

John Snow arrived in London in the autumn of 1836 having travelled from his home in York by a surprising route: he went first to Liverpool and then proceeded on foot through North and South Wales and Bath. In London he enrolled at the famous Hunterian School in Great Windmill Street. A year later he became a student at the Westminster Hospital, recently installed in its new building in the Broad Sanctuary, across the road from the West Door of the Abbey.

On May 2, 1838, Snow satisfied the examiners and was enrolled as a Member of the Royal College of Surgeons. He looked for a house-appointment at his Hospital but discovered that there was a regulation requiring candidates to have "passed Apothecaries' Hall", as the phrase went. He took this examination but by the time this had been done it was October and all the house-offices were filled. He therefore went straight into practice and put up his plate at 54 Frith Street, Soho, a short distance from his student lodgings at 11 Bateman's Buildings.

At first, not unexpectedly, he had much time to spare, and he occupied part of it as a clinical assistant at the neighbouring Charing Cross Hospital. He also took the opportunity to read in the library of the College of Surgeons where it was later said of him that he had been "a quiet man who read slowly and was not too proud to ask for a translation when an original bothered him". The reading he was able to do was put to good purpose; for in 1843 he took the M.B., B.S. of the new University of London and in 1844 his name appeared in the First Division of the M.D.

Such then was the metropolitan scholastic career of John Snow, remarkable for its wide extent—the Hunterian School, the Westminster Hospital, the College of Surgeons, the Society of Apothecaries, Charing Cross Hospital, and the University of London. We must also

recall the basis on which this achievement was founded—the apprenticeship to Mr. Hardcastle of the Newcastle Infirmary (where Snow's name appears in the first list of students in the new Medical School) and the work as general assistant first to Mr. Watson of Burnopfield and later to Mr. Warburton of Pateley Bridge.

As a young doctor with ideas Snow, of course, needed a forum in which to expound them: and this he found in the Westminster Medical Society. Richardson [3], Snow's friend and immediate biographer, tells us that "at first he was very timid and although he always spoke to the point he found it difficult to obtain favourable notice. At first nobody replied to what he had said. After a while some grave counsellor condescended to refer to him as the 'last speaker'. Then someone bolder still 'concurred with Mr. Snow'". All this sounds very natural and to it must be added Snow's own later view that "upon this early connexion with the Westminster Medical depended his continuance in London and all his succeeding scientific success".

In 1849 the Medical Society of London was re-organized to include the Westminster Medical Society. In 1852 Snow was the Orator of the new joint Society; he spoke on "Continuous Molecular Changes more particularly in Relation to Epidemic Disease" [4]. In March 1855 he was inducted as President and visitors to the Society's rooms in Chandos Street may find his name in the list of Presidents which adorns the pilasters of the meeting-room.

Other learned bodies which had the honour of numbering Snow among their members were the Epidemiological Society, the Pathological Society, The British Medical Association, and the Royal Medical and Chirurgical Society, forerunner of the Royal Society of Medicine. Those to which he was most closely attached, however, appear to have been the Medical Society of London and the Epidemiological Society.

Snow's earliest anæsthetic administrations were to the Dental Out-patients at St. George's Hospital and they were so successful that he was almost immediately asked to anæsthetize for major surgery. His first in-patient case was one of ulceration of the cartilage of the ankle-joint and the operation took place on January 14,1847.

Very shortly afterwards he was invited to demonstrate his methods at University College Hospital, where in December 1846, Liston had performed the famous thigh amputation under ether anæsthesia. Liston was at this time in the last months of his life and it is said that he was very much pleased by Snow's manner, by his methods and by their success.

Snow's work at these two hospitals is recorded in his book "On the Inhalation of the Vapour of Ether in Surgical Operations" [5], which he published in September 1847, less than a year after the introduction of ether at Boston.

Probably the most successful and certainly one of the most active surgeons in London in the 1850s was Mr. (later Sir) William Fergusson. Snow became his anæsthetist both in private and at King's College Hospital, then situated in the Aldwych. We read in his case reports that he was also called in upon occasion to Charing Cross Hospital, St. Mark's Hospital, the Orthopædic Hospital and St. James' Infirmary: an almost unrivalled list. In addition he also worked for a period of twenty months at the Brompton Hospital, London, observing the effects of various drugs when given by inhalation. The drugs he tried included morphia, stramonium, hydrocyanic acid and "conia" and his findings were reported at a meeting of the Medical Society of London in 1851 and published in the *London Journal of Medicine* [6].

In the year 1845 Snow had been ill with signs of renal disorder. On his return from a holiday in the Isle of Wight he was appointed Lecturer in Forensic Medicine at the Aldergate Street School of Medicine. This establishment had been opened with the idea of attracting the students of St. Bartholomew's Hospital, but its relations with that hospital seem to have been neither very close nor very happy. The School collapsed in 1849 and Snow with the other teachers was held responsible for the financial deficit which appeared.

It is of interest to note that the hospitals at which Snow was taught were those of Newcastle, Westminster and Charing Cross. Those at which he was regular anæsthetist were St. George's, University College and King's College.

Of the memorials that still remain to us of John Snow the most important are his two masterpieces—"On the Mode of Communication of Cholera" and "On Chloroform and Other Anæsthetics". The "Cholera" was published in its full form in 1855 being largely made up from a pamphlet of 1849 with various subsequent papers. The proof of its quality is to be seen in its re-publication in 1936 by the Commonwealth Fund of America followed by a second re-publication in 1949. The "Chloroform" and the sad story of its all-but-completion by Snow's hand are familiar to all.

Other memorials record his last resting place, and the various places where he lived

and worked. Snow's tombstone is in the Brompton Cemetery, and successive inscriptions recount its history:

TO JOHN SNOW, M.D.
BORN AT YORK
MARCH 15th, 1813
DIED IN LONDON
JUNE 16th, 1858.
IN REMEMBRANCE OF
HIS GREAT LABOURS IN SCIENCE
AND OF THE EXCELLENCE
OF HIS PRIVATE LIFE AND CHARACTER
THIS MONUMENT
(WITH THE ASSENT OF
MR. WILLIAM SNOW)
HAS BEEN ERECTED OVER
HIS GRAVE
BY HIS PROFESSIONAL BRETHREN
AND FRIENDS.

RESTORED IN 1895
BY SIR BENJAMIN W. RICHARDSON, F.R.S.
AND A FEW SURVIVING FRIENDS.

In 1937 a distinguished American anæsthetist was in London and requested Professor Sir Robert Macintosh to take him to see the grave. They found the stone somewhat dilapidated. A small fund was at once organized for its repair, and the following words added:

INSCRIPTION RESTORED IN 1938 BY MEMBERS OF
THE SECTION OF ANÆSTHETICS OF THE ROYAL
SOCIETY OF MEDICINE AND ANÆSTHETISTS IN
THE UNITED STATES OF AMERICA.

In April 1941 a bomb fell very close to the tombstone, which was not a very solid structure, and the explosion caused its almost complete disintegration. Ten years later the Association of Anæsthetists raised a fund and replaced the original by a solid block of Portland stone made in as exact a replica as possible. This new stone with a further appropriate inscription on its base was unveiled by Miss Una Snow on September 6, 1951.

In 1946 the centenary of ether anæsthesia was celebrated, and a commemorative plaque was then installed at the Royal College of Surgeons, bearing on it the names of the four British pioneers of the art and science of anæsthetics—Hickman, Simpson, Snow and Clover.

In his later years Snow lived at 18 Sackville Street, a house now given over to commercial use, and on which, in 1949, the London County Council put up a commemorative plaque. A letter written by Snow from that address to the Secretary of the Royal Institution still exists. It reads—"Dear Sir, I am sorry that you are an invalid and require to undergo an operation, but I shall have much pleasure in calling on you at two o'clock on Friday next in order to administer chloroform and prevent you from having the pain of the operation. Yours very truly, John Snow". This letter found its way back from Albemarle Street to Sackville Street to the shop of Sotheran the bookseller, and is now in the Library of the Medical School of St. George's Hospital at Hyde Park Corner.

Next we come to a somewhat less happy memorial. The site of the famous Broad Street Pump is now occupied by a tavern, known for many years as the "Newcastle-on-Tyne". In 1954, the centenary of the famous cholera epidemic, it was suggested to the L.C.C. that a plaque should be erected. The Council pointed out that such a memorial had already been erected in Sackville Street. The owners of the hostelry came forward, however, and decided to re-name it the "Doctor John Snow" and at the next Brewster sessions this was done. The Snow family, however, were far from pleased at this and considered that it was casting a slur on the great man's memory, for he had maintained a life-long devotion to the cause of temperance. Unfortunately, the protest came too late and the inn in Broadwick Street (as Broad Street is now called) is the "Doctor John Snow" complete with painted sign.

Finally, there is the Snow Medal instituted by the Association of Anæsthetists and awarded to those who by their personal distinction have brought honour to the specialty.

John Snow's bookplate carried his motto—"Vive, ut vivas!" He lived a hundred years ago: his fame is higher and more widespread to-day than it has ever been: and his name will be revered as long as there is a science of Public Health and as long as there is an art of anæsthetic administration.

REFERENCES

1 Snow, John (1849) On the Mode of Communication of Cholera. London.

2 —— (1855) On the Mode of Communication of Cholera. 2nd edit., much enlarged. London.

3 —— (1858) On Chloroform and Other Anæsthetics: Their Action and Administration. Edited, with a Memoir of the Author by Benjamin W. Richardson. London.

4 —— (1853) On the Continuous Molecular Changes, More Particularly in Their Relation to Epidemic Diseases. Being the Oration delivered at the 80th Anniversary of the Medical Society of London. London.

5 —— (1847) On the Inhalation of the Vapour of Ether in Surgical Operations; Containing a Description of the Various Stages of Etherization, and a Statement of the Result of Nearly 80 Operations in which Ether has been employed in St. George's and University College Hospitals. London.

6 —— (1851) On the Inhalation of Various Medicinal Substances. London. *London Journal of Medicine*, **3**, 122.

## John Snow and the Enlightenment

By M. H. Armstrong Davison, M.B.E., T.D., M.D.

*Newcastle upon Tyne*

At the centenary of John Snow's death, we realize that his achievement is recognizably great, even when placed beside the vast knowledge of medicine which has since accumulated: it appears even greater when placed in its true setting—the work and ideas of the era in which he lived.

Snow, born in 1813, was a child of the period which is called the "Enlightenment", which may be considered to have begun in 1754 with the presentation, by Joseph Black, of his doctoral thesis, "On Magnesia Alba and Other Alcaline Substances"; and which came to an end on October 16, 1846, when Morton demonstrated that anæsthesia with ether was a practical reality.

The advances of the "Enlightenment" were not often obvious medical improvements. The work of Priestley, Lavoisier, Auenbrugger and Laennec did little at the time to improve the lot of the patient, while the discovery of vaccination, important as it was, did not lead to any understanding of the processes of disease. At the time of Snow's birth, the only specific curative drugs known were quinine (malaria), ipecacuanha (dysentery) and mercury (syphilis). The many other drugs in the pharmacopœia were of symptomatic benefit only, or of no use at all.

The doctors were ignorant of the cause of disease. Fracastoro, in 1546, had laid down the basis of contagion and infection, and Kircher, in 1658, had attributed plague to an invasion of the body by micro-organisms, but all this had been forgotten. With the overthrow of the classical ideas by such men as Galileo and Newton, the humoral theory of disease was also discarded, but there was nothing to put in its place.

The doctors of John Snow's period were too materialistic to lay the blame for disease upon God, and they were forced, therefore, to admit their ignorance. Consequently, the patients lost faith in their doctors, and the doctors lost faith in themselves. Nor were the doctors in a position to investigate the cause of disease scientifically, for each branch of learning was cut off from its fellows by an almost complete lack of societies and scientific journals. With communications depending on the horse and the sailing-ship, the doctor was separated by an immense gulf from advances, not only in general science, but also in his own particular subject. The doctor, therefore, had to look for the cause of disease within the small horizon which his own eye commanded, and, in this, he was often misled by his ignorance of statistics. These were first successfully employed in the cause of medicine by Louis, when, in 1835, he demolished the theory of Broussais, that bleeding was a suitable remedy for pneumonia.

Naturally, therefore, many doctors constructed for themselves their own systems of medicine, such as Broussais, who decided that gastro-enteritis was the cause of all disease, Cruveilhier, who blamed phlebitis, and Cullen with his theory of nervous irritation. John

Brown claimed that diseases were either sthenic or asthenic; for the former he prescribed a sedative, and, for the latter, a stimulant. Benjamin Rush of Philadelphia went even farther, and developed a theory that all fevers ought to be treated by reducing the excitability of the blood vessels, which he did by strong purges and bleeding to the point of syncope. It was this attitude which created homœopathy, for its inventor had noticed that quinine, which was used in the treatment of fever, would itself produce fever, if given in sufficient quantity. Snow himself was touched, if only slightly, by the same urge, for, like his friend B. W. Richardson, he came to believe, if not that alcohol was the sole cause of disease, yet that it was responsible for a good many of the ills to which the flesh is heir.

These, and other, systematists did great damage to medicine, and their squabbles became the laughing-stock of the public, who at least had knowledge enough to realize that the empty vapourings of the professors lacked all vestige of scientific basis, save a jargon of meaningless words of Greek derivation.

It was to this atmosphere that Snow must have been introduced when, in 1827, at the age of 14, he became the apprentice of Mr. William Hardcastle of Benton, near Newcastle upon Tyne. His duties at first would be confined to the tasks of rolling pills, washing bottles and delivering medicines. Later, he would have been allowed to accompany his master on his visits, and, in time, he would even be permitted to advise the "charity" patients. The treatment given would be the usual purges, vomits, plasters, blood-lettings and draughts, the latter being composed of many evil-tasting and useless galenicals. Every patient who recovered would be claimed as proof that the treatment was correct, but the failures would be forgotten, and, of them it would be said that, if only treatment had begun sooner and had been more drastic, they would have recovered. Nor would Snow have learned anything very different from these accepted methods when he attended the new Medical School in 1832, for this was a very modest undertaking, and by no means a seat of vast learning and research.

When, in 1831, the epidemic of Asiatic cholera broke out, Snow seems to have been given charge of a branch surgery at Killingworth. If it be true that it was during this period that Snow first realized the importance of the water supply in the transmission of cholera, we must acclaim the intellect of this youth of 18, who could make such an hypothesis against the background of a medical science such as we have described. Nevertheless, the period was not without men whose outlook was so different as to stamp them, like John Snow, as the precursors of the new era. Bretonneau and his work on diphtheria; Henry Hill Hickman and his single-handed fight against pain; Richard Bright, whose "Reports of Medical Cases" in 1827 first drew attention to the connexion between disease of the kidneys and dropsy; O'Shaughnessy and his quantitative examination of the blood serum in cholera; Marshall Hall and his discovery of the reflex arc: these were all men who were on the right track, and even they were overshadowed by the advances which, in Snow's day, were taking place in Public Health. All in all, however, the men who were on the right track were few: the adherents of mumbo-jumbo formed the hard core of the medical fraternity; and only time could tell whether any particular concept was right or wrong. This is exemplified by the case of Robert James Graves, who, in 1835, described exophthalmic goitre, for which his name is remembered. He is also the man who asked that his epitaph might be, "He fed fevers", and, in this, we, a century later, know him to have been right. At the time, however, he was but another systematizer, and perhaps this great idea was nothing more than a new treatment, as different as possible from all others, dictated, not by scientific reasoning, but by the wish to found a new doctrine and to set up a following of his own.

Let us now take another look at John Snow: read his three great books and compare them, not with the medical science of our own times, but with the articles published in the *Lancet* in Snow's own day: the discipline will reveal the astonishing grasp of that great man. I refer, in particular, to his work "On the Inhalation of the Vapour of Ether", in which the results of physical experiments on gases and vapours, and of animal behaviour under the influence of ether are correlated with clinical appearances and the description of new apparatus. All this, and yet the book was on sale within a year of the first administration of an anæsthetic.

The year 1858 which saw the death of Snow at the early age of 45, also saw new life appear in the medical profession, for, in that year, the Act of Parliament was passed which established the General Medical Council, and which has led to the benevolent direction of medical education into paths which, if not perfect, have at least served the victims of disease better than could ever have been achieved by the method of apprenticeship to which Snow himself had to submit.

[A "John Snow" book display was arranged by **Dr. Bryn Thomas.**]

## BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

**Allen (C. E.).** Homosexuality: its nature, causation and treatment. pp. 143. London: Staples. 15s. 1958.

**American Association for the Advancement of Science.** Pituitary-adrenal function. pp. 411. Washington: A.A.A.S. $3.50 (32s.). 1950.

**Bellotti (R.), and Ravera (M.).** Il bromo in fisiopatologia. pp. 171. Pisa: Omnia Medica. 1957.

**Bijon (R.).** Traitement chimique du cancer par les oligo-éléments. 2nd ed. pp. 77. Paris: Maloine. 1958.

**British Drug Houses, Ltd.** The B.D.H. guide to the B.P. 1958. pp. 118. London: B.D.H. 1958.

**Bruce (N. E. T.), *et al.*** Physiotherapy in chest diseases. pp. 98. London: N.A.P.T. 1958.

**Cajano (A.), and Bile (G.).** L'immuno-morfologia nello esperimento e nella clinica. (Biblioteca Haematol. XXV.) pp. 203. Pavia: Ediz. di Haematologica. 1958.

**Campbell (J. M.).** From a trade to a profession: byways in dental history. pp. 254. Private circulation. 1958.

**Conferencia Inter-Americana de Medicina del Trabajo.** Primera conferencia, Miami, 3–6 Septiembre 1956. pp. 251. Universidad de Miami. 1957.

**Congresses. Corticotropin.** International conference on standardization of corticotropin. London, 16–18 July 1957. pp. 236. Typescript. 1958.

**Finch (W. E.).** Disinfectants: their values and uses. pp. 188. London: Chapman and Hall. 30s. 1958.

**Hackett (C. J.).** An international nomenclature of yaws lesions. pp. 102. Geneva: W.H.O. 20s. 1957.

**Hartwell (J. L.).** Survey of compounds which have been tested for carcinogenic activity. Suppt. 1. pp. 388. Washington: U.S. Department of Health, Education and Welfare. 1957.

**Hobbs (B. C.).** Certain aspects of food poisoning. Technical Circular No. 131. pp. 8. Leatherhead: British Food Manufacturing Industries Research Association. 1958.

**Horton-Smith (C.), ed.** Biological aspects of the transmission of disease. pp. 184. Edinburgh and London: Oliver and Boyd. 21s. 1957.

**Indianapolis, Central State Hospital.** Psychoses with rheumatic brain disease and other late cerebral sequelae of rheumatic fever. Studies from the Indianapolis Central State Hospital, Vol. 11. Indianapolis: Central State Hospital. 1944.

**Japan Medical Congress.** XIV Japan Medical Congress, 1955. 2 vols. Kyoto: The University. 1955.

**Lendon (N. C.).** Disease among prisoners of war. pp. 58. Typescript. 1951.

**Lomholt (E.).** Home conditions: a sociomedical study of 1,066 hospitalized patients with skin and venereal diseases. pp. 100. Copenhagen: Rosenkilde and Bagger. 1958.

**Smart (G. A.), ed.** Metabolic disturbances in clinical medicine. pp. 358. London: Churchill. 45s. 1958.

**Strauss (E. B.).** Psychiatry in the modern world. pp. 71. London: Joseph. 8s. 6d. 1958.

**Thomas (J. D.).** Hydatid disease. A collection of papers on hydatid disease. Edited by A. A. Lendon. Vol. 2. pp. 166. London: Baillière, Tindall & Son. 1894.

**Williams (D. Innes).** Urology in childhood. pp. 353. Berlin: Springer. 1958.

# Section of Obstetrics and Gynæcology

President—Sir ARTHUR GEMMELL, M.C., T.D., M.A., M.D., Hon. M.M.S.A., F.R.C.S.Ed., F.R.C.O.G.

[*April* 25, 1958]

## An Obstetrical Forceps Using a New Principle of Parallelism

By WALLACE B. SHUTE, B.A., M.D., M.R.C.O.G., F.R.C.S.(C.)

THOUGH the principle of delivery by traction was described by Hippocrates and demonstrated by Avicenna in the eleventh century, it remained for the brilliant Peter Chamberlen to develop the first humane obstetrical forceps known to the western world. Since 1723, when the jealously guarded secret of his instrument was finally revealed to the profession, all modifications of Chamberlen's prototype (and there have been over 600 of these) have been designed to increase the safety or ease of application of this forceps.

During the last 250 years four major alterations of Chamberlen's pattern have been introduced:

(1) The addition of a pelvic curve to the forceps blade by Levret in 1747.

(2) The invention of the English lock by Smellie in 1752.

(3) The introduction of the principle of axis-traction by Tarnier in 1877 to facilitate passage of a high head through the curve of Carus.

(4) The modifications of Kjelland. He incorporated a sliding lock for application to the asynclitic head and, by eliminating the pelvic curve completely to permit easy rotation from transverse positions, returned directly to the straight blade of the first forceps model.

Further minor modifications include the Barton forceps which facilitates rotation from transverse and posterior positions but gives increased difficulty in extraction, and the Piper forceps, designed solely for delivery of the after-coming head. Other less significant variations include the substitution of solid for fenestrated blades, minor changes in the cephalic curve, the use of narrow or wide shanks, and alterations in length, shaping and corrugation of the handles.

It is a well-known medical truism that treatments multiply in the absence of cure: thus many forceps are eloquent of the failure of each. If one forceps could be invented to solve all or most of the problems of instrumental delivery, not only could every obstetrician achieve easy mastery of its use but a gigantic stride would be taken in the direction of safe obstetrics.

The one essential element to any perfect obstetric forceps is that it must fit all foetal heads accurately, from the smallest to the largest size. Hence the blades must approach and separate in exact parallelism. To achieve such a result, measurements were made of the biparietal and bimalar diameters of a large number of newborn infants. On the basis of the astonishing constancy of ratio between these two diameters, a cephalic curve was drawn for the new instrument which would enable it to fit every head accurately whatever its size. The pelvic curve was retained for its proven advantage in guiding the head through the curve of Carus with minimum risk of contamination from the anus during extraction. The shanks were made slightly longer than those of the long De Lee forceps. The lock which proved extremely difficult to develop, was designed to match the complex mechanical needs of a parallel forceps with total efficiency, yet complete simplicity. Such a device must be easy to lock without fumbling, completely rigid when locked, yet capable of instant disengagement at the will of the operator.

The first parallel forceps was developed by the author in 1941 while he was Resident at Cook County Hospital, Chicago, and was tested with his permission on Dr. J. E. Fitzgerald's service there. Since then several defects in the first instrument have been remedied and a new efficient single locking device has been perfected to meet the specific demands peculiar to a parallel forceps (Fig. 1).

Our priority for the use of the principle of parallelism in obstetrical forceps has been established by photographs and descriptions of the first forceps made, notarized in 1941. The present parallel forceps was patented in the United States in 1956 and in Canada in 1958. Patents are pending in Great Britain, various European countries, Japan and the U.S.S.R.



FIG. 1.—Left: De Lee obstetric forceps, with "scissor" lock. Right: the Shute parallel forceps.

In detail, this lock consists of two moving parts imprisoned in the shank and horn of the left forceps shaft, and which may be described as follows:

(1) A double-threaded screw works within a longitudinal bore at right-angles to the axis of the forceps shaft which, when maximally retracted, is recessed within the traction horn of the handle. To prevent uncontrolled rotation the screw is keyed from below and so can move smoothly laterally without turning. Fused to its free end, i.e. that projecting towards the opposing shank, is a rectangular piece of steel forming a T-shape with the axis of the screw.

(2) A large nut or wheel is imprisoned in an axial slot in the left shank. This is deeply notched to allow easy, powerful rotation by the fingers. It is threaded and engaged with the screw, so that it controls all movement of the latter towards or away from the opposing shank.

The technique for use of the parallel forceps is as follows:

The blades are guided into place in cephalic application in the usual manner except that each, being accurately curved, can be inserted almost directly with much less wandering. Either blade can be inserted first, since in the parallel forceps the need for clumsy rotation of one handle about the other has been eliminated.

When the blades have been applied to the head, the heels of both handles are automatically forced together. The notched wheel in the left shank is now turned in an anti-clockwise direction until the rectangular T-piece of the screw enters a receptor slot at the junction of the right shank and upper handle. By continued rotation of the wheel the T-piece is forced along an inclined entrance, thus separating the handles gradually until, when it sinks into the final vertical recess in the right shank the forceps has attained exact parallelism. Then a pin, working in a vertical slot in the right shank, is drawn down to catch the upper arm of the T-piece and fix it, thus locking the blades rigidly in parallelism.

Next, the blades which are now merely in apposition with the head, must be tightened upon it to prevent slipping when traction is applied during delivery. They must not, however, be tightened more than the minimal amount required to resist the required traction, since otherwise they could seriously damage intracranial structures. By careful testing, the degree of tightening to achieve this end has been estimated. One complete turn of the wheel moves the screw through a distance of 4 mm. Hence each of the six notches of the wheel corresponds to a linear movement of 0·67 mm. of the screw. Therefore, to tighten the forceps on the head sufficiently to resist any ordinary traction, the wheel is reversed and turned in a clockwise direction through a distance of three notches. This approximates the blades a distance of 2 mm. For very difficult extractions, the wheel may be turned through four or even five notches, thus tightening the blades upon the head by 2·8 to 3·5 mm. If these rules are properly observed, all but the slightest pressure marks upon the face should be avoided in even the most difficult deliveries.

The present parallel forceps has been tested extensively by the author, and on the Obstetrical Service of the Cook County Hospital, Chicago, upon all sizes of fœtal head presenting in all positions. From the results of these practical trials the advantages of this instrument over the usual scissors forceps appear to be as follows:

(1) It maintains accurate parallelism of its blades when applied to fœtal heads varying from the smallest to the largest size.

(2) The blades fit each head exactly, disseminating their pressure equally along the whole area of contact and hence do no violence to cranium, face or skin.

(3) The blades are narrower than those of the usual scissors forceps. Because their cephalic curve is much straighter, application of each blade is therefore easier and requires a minimum of wandering.

(4) The full pelvic curve, important in avoiding contamination during delivery, has been retained. However, it can afford to be, and is, much shorter. Thus it permits rotation of the head from any position with a straight twisting movement, i.e. without the usual compensatory rotation of the handles through a wide arc.

(5) The forceps can be applied to any head in any position. The right blade can be applied first as easily as the left. Its long shank makes it as useful as the Piper forceps for management of the after-coming head of a breech yet it is equally applicable to a high mid-forceps operation.

(6) The mechanism of the lock is extremely simple—just two moving parts which can be articulated and separated with the greatest ease. The forceps can be sterilized by all the standard methods.

(7) As far as possible, the usual shape of the obstetrical forceps tested by time and usage has been maintained. In the parallel forceps the handles not only can, but should be grasped firmly during extraction. No amount of compression of the handles after locking can alter pressure on the fœtal head to the slightest degree.

In the management of the asynclitic head in occiput transverse positions, the following technique has proven effective: The anterior blade is first reversed, inserted posterior to the head and rotated smoothly around the occiput to take up its correct cephalic position. The posterior blade is then inserted directly. However, because of asynclitism and the normal obstruction of the promontory, it will be found to lie at a much lower level in the pelvis than the anterior blade. Firm pressure on the fundus is next applied by an assistant, thus forcing the fœtal axis strongly downwards. This drives the head more deeply into the pelvis, correcting its position physiologically and allowing the blades to become exactly parallel. The lock can then be closed accurately and traction applied safely. This manœuvre when properly performed ensures correct cephalic application in even the most difficult O.P. positions. Indeed, so effective is the method that if asynclitism is not corrected by it, the labour should be carefully reconsidered with a view to its termination by Cæsarean section.

The lesions such as intracranial damage, skull fractures, nerve paralyses and permanent scarring of the face which may follow the use of the scissors forceps in all its current modifications, necessitate a major reform in this vital instrument. The new parallel forceps offers a radical change in basic concepts of construction and application to cure the defects of the existing obstetrical forceps. It is to be hoped that, in presenting a solution by one instrument of the difficulties of many, a very real contribution may be made towards the achievement of safety in parturition.

SUMMARY

(1) A brief survey of the historical development of major principles in the obstetrical forceps has been given.

(2) Basic criteria for the theoretically perfect forceps have been suggested.

(3) A new type of obstetrical forceps is described which introduces for the first time in 350 years the principle of parallel application of blades with a summary of its development, description of its construction and technique of usage.

(4) The advantages of the parallel forceps over the usual scissors forceps are briefly discussed.

THE following specimens were shown:

**Müllerian Agenesis with Adenomyosis.**—Mr. E. A. J. ALMENT.

**Hydrops Fœtalis and Severe Toxæmia at 22 Weeks Pregnancy.**—Mr. DAVID BROWN.

**Prolapse of the Placenta.**—Miss E. COATES.

**Two Cases of Vasa Prævia Successfully Treated by Cæsarean Section.**—Mr. F. J. COCKERSOLE.

**Granulosa Cell Tumour Complicating Pregnancy.**—Mr. LYNN A. J. EVANS.

This tumour was associated with a pregnancy, which aborted at the fourteenth week, and was removed subsequently.

**Primary Vaginal Sarcoma.**—Mr. D. W. S. GORDON.

**Mermaid Fœtus (Sirenomelia).**—Mr. J. C. HARTGILL.

**Congenital Heart Block Associated with an Interventricular Septal Defect (Diagnosed Antepartum).**—Mr. P. J. HUNTINGFORD.

**Two Cases of Primary Malignant Melanoma of the Urethra.**—Mr. G. D. PINKER and Mr. DAVID SAVAGE.

[*May* 30, 1958]

## DISCUSSION ON NEONATAL DEATHS

**Dr. G. R. Osborn** (Derbyshire Royal Infirmary):

*Secondary Causes of Death in the Fœtus and Newborn*

Prematurity should not be given as the cause of death though it may be incompatible with life. Even in quite early embryos the cause of death may be found by microscopic examination. Frequently the lesions found are secondary to abnormalities of the placenta or mother. Notable among these is asphyxia. From a very early stage the embryo will attempt to breathe if the oxygen supply from the mother is insufficient (Fig. 1). For this reason many prefer to speak of anoxia. Because the perivascular hæmorrhages ("Tardieu's spots") follow extreme capillary dilatation due to accumulation of metabolites it is better to use the term asphyxia. In its literal meaning asphyxia is entirely wrong; it means absence of a pulse and the hæmorrhagic phenomena of asphyxia must depend on the presence of a pulse. It is better to speak of "asphyxial hæmorrhages" than Tardieu's spots.

Asphyxial hæmorrhages are of very wide distribution. They are best known in the pleuræ, pericardium and thymus. Functionally active parts are more affected than parts developing late. Their occurrence in the nervous system will be referred to later. They have not been found in the eyes, but sometimes occur in the internal ear. They are almost constant in the parotid glands; this is partly traumatic because of the relationship to the mandible. In the asphyxial state trivial injuries may result in large hæmorrhages. They are found occasionally in the larynx and thyroid. Especially in early embryos they may be large in the right lung and absent in the left, they do not depend on whether it was a live or still birth. The stomach commonly shows trivial hæmorrhages in mucosal folds, rarely these are massive and extend through the submucosa and muscularis; these may ulcerate but such lesions are not peptic ulcers. The pancreas is not often affected; when it is, asphyxial hæmorrhages may be confined to the islets of Langerhans. The breast is an extremely variable organ in the newborn, it may be so small that it is found for study with the greatest difficulty, it may be quite large and contain massive hæmorrhages. This great variation may be of significance much later in life. Hæmorrhages in the testes are very common and are probably correlated with the mechanism for descent, they may be found in testes in any position. Hæmorrhage in the ovaries is extremely rare; the frequent finding of graafian follicles at birth shows functional activity but only once, after examining ovaries from hundreds of neonates, have I found hæmorrhages. These were in one ovary of an anencephalic baby. In the adult the conditions associated with ovarian hæmorrhage are mainly corpora lutea and endometriomata, these are never seen in the fœtus and newborn. Hæmorrhages are curiously rare in the uterus, only occurring in about 1%. The best example of the relationship of hæmorrhage to function is shown in the kidney. Asphyxial hæmorrhages are confined to the juxtamedullary region of the cortex and to the medulla. They are not seen near the capsule where glomeruli are developing and still functionless. The renal lesions are not unlike those of shock nephrosis in adults. The blood urea may rise by about 20 mg. every twelve hours, so far one above 180 mg. per 100 ml. has not been found but it must be possible for an occasional baby to die of uræmia from this nephrosis. Renal cortical hæmorrhages are found on occasion but are traumatic and associated with rupture from the injuries of criminal abortion, etc. Hepatic hæmorrhages are mostly traumatic and may be associated with large tears, sometimes these result from artificial respiration.

*Inhaled substances.*—If the fœtus is asphyxiated it will attempt to breathe and swallow, like someone drowning in later life. The substances inhaled will be (1) those already in the mouth, nose and pharynx, being the secretions or desquamations of these parts, and (2) the various fluids or air found immediately external to the mouth and nose. A large collection of vernix and cornified squames (without nuclei) may be found in the anterior part of the nose (Fig. 2) where they originate. This, and not the skin, is the probable source of the fat found in varying quantity in the hyaline or alveolar duct membrane. Some pus may originate from the turbinate region but if present it has usually been inhaled. Most of the squames found inhaled in the lungs are nucleated (Fig. 3) and originate in the transitional epithelium of the oropharynx. Probably the most important substance in the nose, mouth and throat is mucus. It varies in amount and viscosity. I consider it the basic constituent of the hyaline membrane, a structure of complex and somewhat variable composition.

By far the best dilator of alveoli is liquor amnii. If the fœtal mouth and nose have free access to this its inhalation gives rise to a characteristic and diagnostic appearance (Simpson, 1953, p. 14, Fig. 7). Squames and other substances are suspended in this liquor but are relatively inconspicuous. If the membranes have ruptured and there has been passage of much meconium-stained liquor the lung appearances are different. Figs. 4 and 5 show

that large epithelial fragments, squames, mucus, meconium, liquor and blood may all be found in varying but considerable amount. This blood is presumably maternal and derived from the region of the placenta. In a 7 cm. fœtus its maternal origin was clear from the red cell diameter being only about half that of the erythrocytes in the fœtal vessels near the developing bronchi (Fig. 6); this useful sign does not last very long unfortunately, and especially late in pregnancy the maternal red cells may be swollen and so misleading.

The mouth and nose of the fœtus may be in contact with a large purulent exudate on the placenta, this may or may not be bacterial in origin. The fœtus may inhale and swallow this pus which will be found mixed with squames, etc., in the œsophagus and lungs (Figs. 7 and 8). It was thought that a comparison of this exudate with that on the placenta would establish its origin. The irregular mixing of different types of exudate on the placenta did not permit conclusions being reached when the pus in the œsophagus was different from that in the lungs. If the fœtus is exposed to a purulent exudate for some days it may take in so much that the whole lumen from the nose and mouth to the anus is filled with pus though the mucosæ are free from inflammation (Figs. 9, 10, 11). This 19 cm. fœtus has a histological pneumonia, hence we must ask if such a lesion is (1) the result of being "drowned" in pus, (2) a true pneumonia due to organisms reaching the fœtal lungs from the mother's blood via the placenta, or (3) the result of inhaling infected liquor amnii or other substances. The problem is too complex to state what proportion of histological pneumonias in the fœtus fall into each of these three groups. Many are undoubtedly "drowning" in pus, recognition of these is aided by finding mature and degenerate pus cells in the alveoli, and pus in the nose, œsophagus and perhaps the remainder of the alimentary tract. The problem is not simple because one 30 cm. fœtus which appeared to have been so drowned in pus was found to have an acute lymphadenitis of the mediastinal nodes. Some authorities deny the existence of pneumonia due to organisms reaching the fœtal lungs via the umbilical vessels but some cases appear conclusive. Fig. 12 shows a pneumonia in a 9 cm. fœtus which was an ectopic gestation in the fallopian tube; there can be no possibility of this resulting from early rupture of the membranes. The most important conditions in the mother which may be associated with bacteriæmia are pyelitis, "influenza" which usually means bronchitis, pneumonia or pharyngitis, and dental abscesses. Such maternal episodes have been followed in several days by vaginal hæmorrhage, and by the abortion of a fœtus with pneumonia in about a week. Fig. 13 shows such a pneumonia following pyelitis in the mother, coliform bacilli can be recognized in the alveolar exudate. The bacteriology of most of these cases is unsatisfactory, the fœtus is commonly received in formalin and study by Gram's method only is possible. When culture is possible the organisms obtained are nearly always of the pneumococcus, *Streptococcus viridans* or coliform groups; their significance is thus uncertain until the histological examination is completed. If the fœtal lungs are infiltrated with eosinophils, or show interstitial inflammation in addition to the pus in the alveoli, there is a strong presumption of infection by the blood stream. In syphilis and tuberculosis if the fœtus is affected the placenta is also; the same may be true for the organisms of acute inflammation. There must therefore be some doubt about the route taken from the placenta to the lungs of the fœtus. It is quite certain that rupture of the membranes is not necessary. The importance of early rupture of the membranes in the ætiology of fœtal pneumonia has been exaggerated. It did appear important in the case of a 20 cm. twin fœtus. The first twin was 23 cm. long, injuries indicated that its abortion was due to interference. Four days later the second was born alive but with an extensive histological pneumonia and pus filling the œsophagus, stomach, duodenum and some of the jejunum. This was "drowning" in pus. In a small series in which fœtal injuries were taken as the evidence for criminal instrumental abortion the incidence of histological fœtal pneumonia was only 1 in 8, exactly the same as in large series. Inhalation of infected liquor amnii must be of importance but must not be thought the only ætiology of fœtal pneumonia.

*Cerebral and spinal hæmorrhages.*—The fœtus drowned in pus, shown in Figs. 9, 10 and 11, was also found to have a subarachnoid cerebral hæmorrhage though there was no evidence of head injury. This and many other cases raise doubts about cerebral hæmorrhage as the real cause of death. First, faulty autopsy technique readily leads to false diagnoses of cerebral hæmorrhages; secondly, many appear of asphyxial origin and are due to the real cause of death; thirdly, there is the traumatic group of obvious importance. Because this is such a difficult study in the brain it was decided to investigate the spinal cord which is not so subject to the forces of moulding. The entire vertebral column was removed and the cord and its meninges sectioned with the surrounding structures. The results are set out in Table I. It is clear that hæmorrhages into the spinal cord, in the sub- and extra-dural spaces, and into the posterior root ganglia all occur with considerable frequency. Many are of asphyxial type. Most would have been of no clinical significance had the baby survived but in some there is serious cord damage (Fig. 14). There is no close correlation

TABLE I

SPINAL HÆMORRHAGES—FŒTUS

| No. | Length | In cord | Subdural | Extradural | P. root gang. | Cerebral |
|---|---|---|---|---|---|---|
| 1 | 5 cm. | 0 | 0 | 0 | 0 | 0 |
| 2 | 6 cm. | 0 | 0 | 0 | 0 | 0 |
| 3 | 6 cm. | 0 | ++ | 0 | 0 | 0 |
| 4 | 7 cm. | 0 | + | ++ | +++ | – |
| 5 | 7 cm. | 0 | 0 | 0 | ++ | – |
| 6 | 7 cm. | 0 | 0 | 0 | 0 | 0 |
| 7 | 7 cm. | +PMS | + | + | 0 | – |
| 8 | 9 cm. | 0 | 0 | 0 | 0 | 0 |
| 9 | 9 cm. | 0 | + | 0 | 0 | +LV |
| 10 | 10 cm. | 0 | 0 | 0 | 0 | – |
| 11 | 11 cm. | +AMS | + | + | 0 | – |
| 12 | 12 cm. | +AMS | ++ | ++ | +++ | – |
| 13 | 12 cm. | 0 | 0 | 0 | 0 | +SD |
| 14 | 12 cm. | +PC | 0 | 0 | 0 | + |
| 15 | 13 cm. | ++LC | + | 0 | 0 | +SA |
| 16 | 13 cm. | 0 | 0 | 0 | + | – |
| 17 | 13 cm. | 0 | + | + | – | +SA |
| 18 | 14 cm. | 0 | 0 | 0 | 0 | – |
| 19 | 15 cm. | 0 | 0 | 0 | – | – |
| 20 | 15 cm. | 0 | + | 0 | 0 | – |
| 21 | 15 cm. | +AMS | ++ | ++ | 0 | – |
| 22 | 16 cm. | 0 | 0 | 0 | 0 | – |
| 23 | 17 cm. | 0 | + | 0 | 0 | – |
| 24 | 18 cm. | 0 | 0 | 0 | 0 | 0 |
| 25 | 18 cm. | +PC | + | + | ++ | ++LV |
| 26 | 20 cm. | ++ | + | 0 | 0 | – |
| 27 | 20 cm. | 0 | 0 | 0 | 0 | – |
| 28 | 22 cm. | 0 | 0 | + | + | +SA |
| 29 | 23 cm. | 0 | 0 | 0 | 0 | 0 |
| 30 | 23 cm. | 0 | 0 | 0 | 0 | 0 |
| 31 | 24 cm. | 0 | 0 | + | – | – |
| 32 | 24 cm. | 0 | 0 | 0 | – | – |
| 33 | 24 cm. | 0 | 0 | 0 | – | 0 |
| 34 | 25 cm. | 0 | 0 | 0 | – | – |
| 35 | 25 cm. | 0 | 0 | 0 | +++ | – |
| 36 | 25 cm. | +AMS | + | 0 | – | 0 |
| 37 | 30 cm. | 0 | 0 | ++ | – | – |
| 38 | 32 cm. | +AMS | 0 | 0 | – | +SA |

SPINAL HÆMORRHAGES—NEWBORN

| No. | Hours | In cord | Subdural | Extradural | P. root gang. | Cerebral |
|---|---|---|---|---|---|---|
| 1 | 5 | 0 | 0 | 0 | 0 | – |
| 2 | 6 | 0 | + | + | 0 | – |
| 3 | 6 | 0 | 0 | 0 | – | 0 |
| 4 | 7 | 0 | 0 | ++ | 0 | 0 |
| 5 | 8 | 0 | + | +++ | – | +IV |
| 6 | 8 | 0 | + | + | – | +SA |
| 7 | 9 | 0 | 0 | +++ | 0 | +SD |
| 8 | 9 | 0 | 0 | +++ | – | – |
| 9 | 11 | +PMS | + | +++ | 0 | 0 |
| 10 | 11 | 0 | 0 | +++ | 0 | 0 |
| 11 | 12 | 0 | 0 | 0 | 0 | – |
| 12 | 15 | ++G, PC | + | + | – | 0 |
| 13 | 32 | +AMS | + | ++ | + | 0 |
| 14 | 33 | 0 | + | +++ | – | +SD, +++ |
| 15 | 33 | 0 | + | ++ | 0 | 0 |
| 16 | 43 | 0 | 0 | + | – | 0 |
| 17 | 44 | 0 | ++ | + | 0 | – |
| 18 | 45 | 0 | +++ | + | 0 | +++SD |
| 19 | 60 | +CC | ++ | + | 0 | – |
| 20 | 72 | 0 | + | +++ | 0 | +SA |

PMS = Posterior median sulcus. AMS = Anterior median sulcus. PC = Posterior columns. LC = Lateral columns. LV = Lateral ventricle. SD = Subdural hæmorrhage. SA = Subarachnoid hæmorrhage. G = Grey matter. CC = Central canal.

with cerebral hæmorrhages, either may occur without the other, both may be affected. Lumbar puncture is not a valid method for diagnosing cerebral hæmorrhage. The best example of the secondary nature of both cerebral and spinal hæmorrhage was in a 12 cm. fœtus delivered surgically, the placenta showed both macroscopic and microscopic appearances of hydatidiform mole, a condition incompatible with good oxygenation of the fœtus and possibly the explanation for all the fœtal red cells still being macro-normoblasts. The lungs showed subpleural asphyxial hæmorrhages of these nucleated red cells. There were multiple small asphyxial cerebral hæmorrhages (Fig. 15) to some of which there was a macrophage reaction indicating that they had been present at least a few days before the surgical intervention. The spinal cord had a hæmorrhage of nucleated red cells into the posterior columns (Fig. 16).

*Mechanisms for eliminating air from lungs.*—Many pathologists have been humiliated by diagnosing at autopsy stillbirth in a baby known to have lived and breathed for a considerable time (Taylor, 1928). Because the lungs were airless it was concluded that the baby had lived this length of time on oxygen absorbed from parts other than the lungs. There are two important mechanisms by which air can be expelled from the lungs after they have been expanded by it. The first is valvular (Fig. 17) as described by Jackson and Jackson (1945). The second and more important is acute pulmonary œdema. This lesion is almost confined to live births and may or may not be associated with hyaline membrane in the alveolar ducts. A hæmorrhagic form with membrane is shown in Fig. 18. The false belief that these babies had been absorbing air from their alimentary tracts was partly responsible for treatment by intragastric oxygen. There is no doubt that excellent results follow brief treatment with intragastric oxygen in many babies. The dangers of its prolonged use appear to be little known. There is a wide difference between the comparative safety of leaving an intragastric tube in position for a considerable time for feeding a well-oxygenated premature baby, and the danger of intubating the œsophagus of an asphyxiated baby. The triple response of Lewis following congestion makes certain that there is no such thing as a catheter soft enough for the œsophagus of an asphyxiated infant.

*Œsophageal ulceration.*—Table II shows that ulceration is never found in the œsophagus

TABLE II.—ŒSOPHAGUS: 232 CASES

| | | | |
|---|---|---|---|
| 1 | Embryo-fœtus: 1 cm.—36 cm. .. | 80 | 0% ulcerated |
| 2 | Stillbirths .. .. .. .. | 24 | 0% ulcerated |
| 3 | Outside live births .. .. .. | 15 | 0% ulcerated |
| 4 | Nursing home, L.B., before $I.G.O_2$ | 21 | 14% ulcerated |
| 5 | Nursing home, L.B., no $I.G.O_2$ .. | 21 | 10% ulcerated |
| 6 | Nursing home, L.B., $I.G.O_2$ .. | 71 | 71% ulcerated |

L.B. = Live birth. Before $I.G.O_2$ = Cases studied before treatment by intragastric oxygen had been introduced. No $I.G.O_2$ = said not to have been treated with intragastric oxygen. $I.G.O_2$ = known to have been treated with intragastric oxygen.

of the embryo, fœtus or stillborn baby. It is an acquired lesion with an ætiology which is certainly not shock. Acute inflammatory and peptic ulceration may be found in the œsophagus, the histology is characteristic and quite different from that which follows the passage of tubes. Five appearances are found. Fig. 19 shows the normal stage regularly found in the fœtus, though on occasion the second stage of congestion possibly with asphyxial hæmorrhages but without lesions of the epithelium is found. The third stage is pressure atrophy of the epithelium leading to ulceration with congestion and a variable amount of hæmorrhage; sometimes the hæmorrhage is very large and extends through the whole of the main muscle coats (Fig. 20). In the fourth stage the inflammatory exudate appears, in the worst cases this is associated with gangrene (Fig. 21). In the fifth and final stage bacterial masses are obvious on the surface, these are commonly staphylococci and may be swallowed in vast numbers (Fig. 22). This form of ulceration is not peculiar to the œsophagus of the newborn, it was first recognized because it is virtually the same as the lesion which develops in the prostatic urethra when a catheter is tied in; it is also reproduced in the trachea when a tracheotomy tube has to be left in place for days to treat cases of tetanus.

My main study of œsophageal ulceration has been made in babies from the premature unit where tubes have to be passed into the stomach for a variety of reasons. Table II shows that ulceration is not to be expected in simpler surroundings (outside live births) where tubes are not passed, though it could be found for other reasons on occasion. Table III shows the steep rise in incidence after the introduction of treatment by intragastric oxygen. Table IV shows that in a rough way the incidence of ulceration is proportional to the duration of the treatment, In a further series of 29 cases the time of treatment was systematically reduced and less damage was done to the œsophagus. Actually the results are

TABLE III

| Œsophagus | 21 cases Before $I.G.O_2$ | | 21 cases No $I.G.O_2$ | | 71 cases $I.G.O_2$ | |
|---|---|---|---|---|---|---|
| Normal | 18 | =86% | 14 | =90% | 9 | =29% |
| Congestion + hæmorrhage | 0 | | 5 | | 11 | |
| Ulcers + hæmorrhage | 0 | =14% | 1 | =10% | 24 | =71% |
| Ulcers + inflammatory exudate | 3 | | 1 | | 20 | |
| Ulcers + inflammatory exudate + bacterial masses on the surface | 0 | | 0 | | 7 | |

Before $I.G.O_2$: ulcers (*a*) peptic (*b*) followed treatment with alcohol and chloral for convulsions.
No $I.G.O_2$: ulcers followed intubation.

TABLE IV.—DURATION OF $I.G.O_2$ IN THE 71 CASES

| Cases | Hours Under 2 | 2–4 | Over 4 |
|---|---|---|---|
| 9 Œsophagus normal | 9 | 0 | 0 |
| 11 Congestion and hæmorrhage | 7 | 3 | 1 |
| 24 Ulceration and hæmorrhage | 8 | 5 | 11 |
| 20 Ulceration and inflammatory exudate | 3 | 1 | 16 |
| 7 Ulceration, exudate, bacterial masses | 1 | 0 | 6 |

DURATION OF $I.G.O_2$ IN THE 29 CASES

| | Hours Under ½ | ½–1 | 1–2 | 2–4 |
|---|---|---|---|---|
| 1 Œsophagus normal | 1 | 0 | 0 | 0 |
| 6 Congestion and hæmorrhage | 1 | 3 | 1 | 1 |
| 10 Ulceration and hæmorrhage | 2 | 3 | 4 | 1 |
| 10 Ulceration and inflammatory exudate | 2 | 2 | 1 | 5 |
| 2 Ulceration, exudate, bacterial masses | 0 | 1 | 0 | 1 |

Note: There is doubt about the duration of treatment by intragastric oxygen in some of the cases, especially in the earlier group of 71. This is not enough to affect the conclusions.

better than indicated by Table IV, for many only just reached the more advanced pathological stage. It is still clear, however, that time is not the dominating factor, it is something in the condition of the baby which I believe to be asphyxia. This is very unfortunate because it means that the greater the need for this treatment the more dangerous it becomes. Table V

TABLE V.—ASSOCIATED LESIONS IN 71 + 29 CASES TREATED WITH $I.G.O_2$

| | Normal | | Congested | | Early ulceration | | Late ulceration | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | *71* | *29* | *71* | *29* | *71* | *29* | *71* | *29* | |
| Membrane | 3 | 1 | 4 | 4 | 4 | 4 | 6 | 5 | 31 |
| Membrane + cerebral hæmorrhage | 1 | 0 | 1 | 1 | 6 | 1 | 5 | 1 | 16 |
| Membrane + pneumonia | 1 | 0 | 0 | 1 | 0 | 1 | 7 | 1 | 11 |
| Pneumonia | 3 | 0 | 2 | 0 | 6 | 1 | 8 | 2 | 22 |
| Cerebral hæmorrhage, heart, etc. | 1 | 0 | 4 | 0 | 8 | 3 | 1 | 3 | 20 |
| | 9 | 1 | 11 | 6 | 24 | 10 | 27 | 12 | 100 |

is an unsatisfactory attempt to prove the importance of the asphyxial element. It does appear from this that less damage is done in the miscellaneous group of heart failure, etc., than in the groups with severe lung lesions. It is also clear that intragastric oxygen is not the treatment for hyaline membrane and other serious lung conditions. The most important form of treatment must be prevention; this implies that the problem is primarily for the obstetrician.

*Hæmorrhagic lungs in the newborn.*—One of the babies in the second group of 29 cases shown in Table IV was given intragastric oxygen with some success at the time of birth, and again for 45 minutes before death three days later. Ulcerations of the œsophagus were clearly of two ages, the older ulcers had an organizing inflammatory exudate, the recent ones were little beyond the stage of congestion and pressure atrophy. The lungs were dark red and generally consolidated. The alveoli were packed with red blood cells, these also filled much of the bronchial tree. Membrane was present but was nearly all free in the terminal bronchioles, it was not in the position of the common alveolar duct hyaline membrane but gave the histochemical reactions for this. These hæmorrhagic lungs in the newborn are a difficult problem. They are not pneumonia in the stage of red hepatization. They fall into at least three groups. The largest group is secondary to hyaline

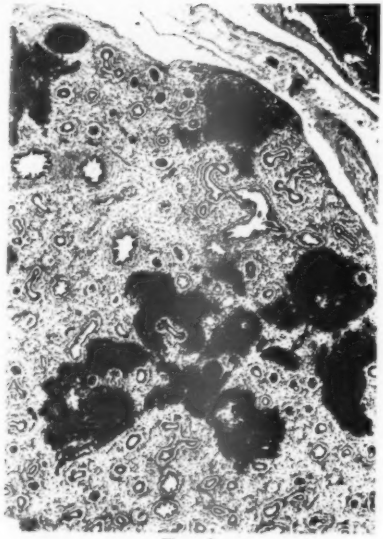


FIG. 1.

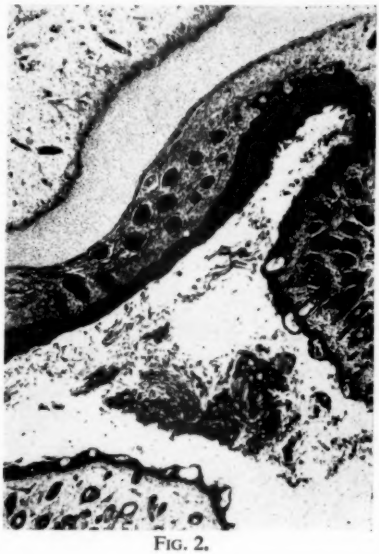


FIG. 2.

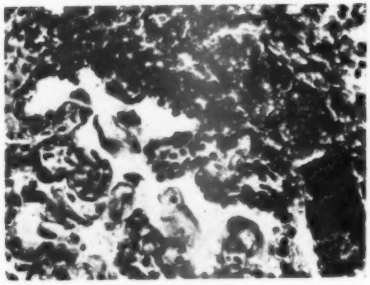


FIG. 3.

FIG. 1.—Asphyxial hæmorrhages in the lung of a 9 cm. fœtus (12 weeks.) × 75.

FIG. 2.—Mass of cornified squames (no nuclei) and vernix in the nose of a 24 cm. fœtus. This is the desquamation and secretion of the related epithelium, it is not inhaled. × 30.

FIG. 3.—Nucleated squames in the alveoli of a 24-week fœtus. The origin of an asphyxial hæmorrhage is well shown. Case of placenta prævia. Stillbirth. × 300.

membrane; inspissated blood from the alveolar capillaries displaces the membrane from its typical position in the alveolar ducts and so makes the diagnosis obscure. The next largest group is secondary to cerebral lesions and is a neurogenic hæmorrhagic acute pulmonary œdema. A third group, fortunately rare, results from the transfusion of too large a volume of blood.

*Cæsarean section syndrome.*—There is no doubt that in many centres the mortality among babies delivered by Cæsarean section is high, and that "Cæsarean section syndrome" is hyaline membrane. A careful record of the factors responsible for this syndrome will eventually solve the nature of hyaline membrane. Anæsthetics have been blamed but their influence is likely to be asphyxial; there are unpublished reports of the disappearance of the Cæsarean section syndrome with local instead of general anæsthesia. The sudden division of the cord in a partially asphyxiated baby must favour the inhalation of the mixture of mucin, squames, vernix, etc., present in the nasopharynx of the baby. We have seen the syndrome disappear at the Derbyshire Hospital for Women when great care was taken to prevent this occurrence; these cases too are unpublished. An excellent series demonstrating the same points is that of Strang *et al.* (1957). The only criticism of their procedure is the one made at the meeting of the Birmingham and Midland Obstetrical and Gynæcological Society on June 4, 1958: babies may be lost if the toilet of the mouth and larynx is allowed to wait until the cord ceases pulsating.

*Interstitial pulmonary emphysema and pneumothorax.*—Babies born naturally or by Cæsarean section may die within about a day from interstitial pulmonary emphysema and pneumothorax. This probably has a variety of causes but the outstanding one is the

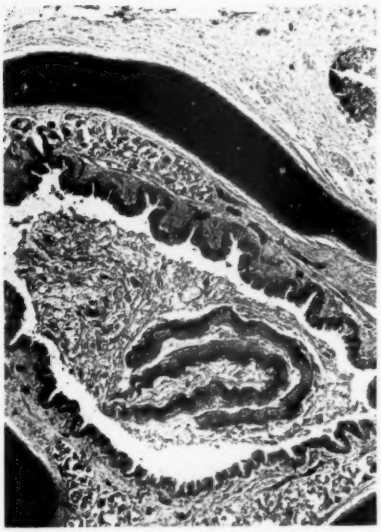


FIG. 4.

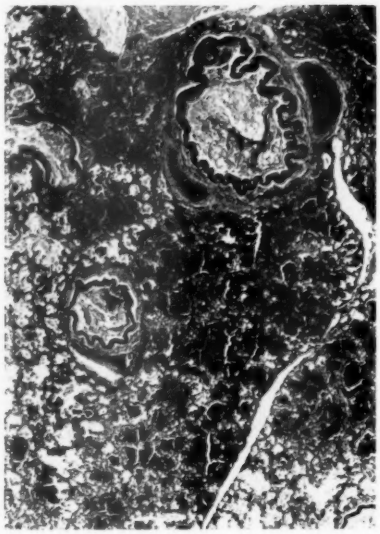


FIG. 5.

FIG. 4.—Fragments of stratified squamous epithelium, squames, meconium and other substances nhaled into the bronchus of a full-term stillborn baby. × 30.

FIG. 5.—Same case as Fig. 4. Mucus, meconium and squames in the bronchi and bronchioles. Alveoli to the lower right and the left part of the picture dilated by liquor amnii, most others dilated by blood which is probably maternal. All the meconium had been passed from the large bowel. × 75.

FIG. 6.—Maternal blood inhaled into the bronchi of a 7 cm. fœtus. These red cells have a diameter of about 7 $\mu$ and contrast with the large red cells of the fœtus indicated by the arrows. The differentiation of maternal and fœtal red cells by size becomes unreliable after the early stages of pregnancy. × 300.

FIG. 7.—Pus and squames in the œsophagus of a 29 cm. fœtus. The normal mucosa indicates that they have been swallowed, they usually come from a purulent exudate in the placenta and membranes, and need not be bacterial in origin. × 75.

FIG. 8.—Histological pneumonia in fœtus whose œsophagus is shown in Fig. 7. This is not a true pneumonia but "drowning" in pus. × 75.

FIG. 9.—Pus around the turbinates, nose of a 19 cm. fœtus. Pus filled the nose, pharynx, lungs, and the whole alimentary canal. × 30.

FIG. 10.—Pus filling the small bowel of the 19 cm. fœtus shown in Fig. 9. Note absence of mucosal inflammation. × 30.

FIG. 11.—Pus filling the rectum of the fœtus illustrated in Figs. 9 and 10. All the meconium has been displaced by it. × 2.

ballooning of the alveolar ducts and terminal parts of the respiratory bronchioles when the alveoli are not expanded (Simpson, 1953, Figs. 27 and 35). By far the most important cause of this ballooning is hyaline membrane in the alveolar ducts. Fig. 23 shows this in very low power with spontaneous rupture in a baby delivered by Cæsarean section. Fig. 24 shows the gross appearances in a baby whose poor respiratory efforts were aided by mouth-to-mouth breathing; the immediate response to this was good but it almost certainly ruptured ballooned alveolar ducts and so caused death from double pneumothorax.

The obstetrician is thus the experimental pathologist. He will prove the ætiology of hæmorrhagic lungs in the newborn, the Cæsarean section syndrome, and pulmonary interstitial emphysema by showing how to abolish them.

## REFERENCES

JACKSON, C., and JACKSON, C. L. (1945) Diseases of the Nose, Throat and Ear. Philadelphia and London; p. 625.

SIMPSON, K. (1953) Modern Trends in Forensic Medicine. London.

STRANG, L. B., ANDERSON, G. S., and PLATT, J. W. (1957) *Lancet*, i, 954.

TAYLOR, A. S. (1928) Principles and Practice of Medical Jurisprudence. 8th edit. Edited by Sydney Smith. London; **2**, 196.

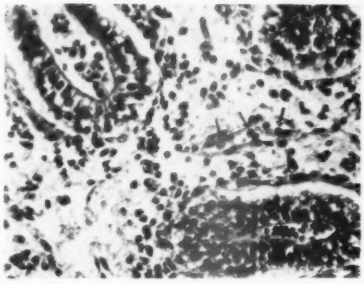


FIG. 6.

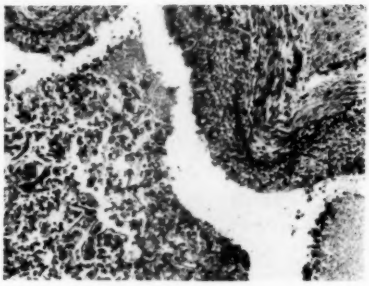


FIG. 7.

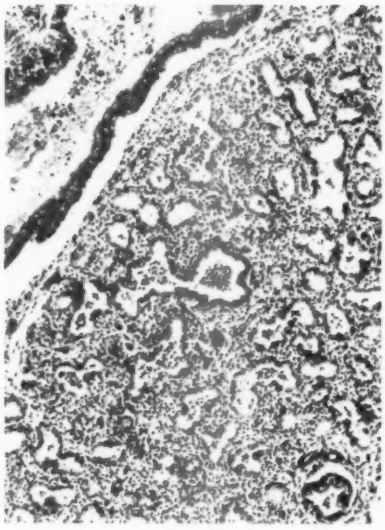


FIG. 8.



FIG. 9.



FIG. 10.



FIG. 11.



FIG. 12.

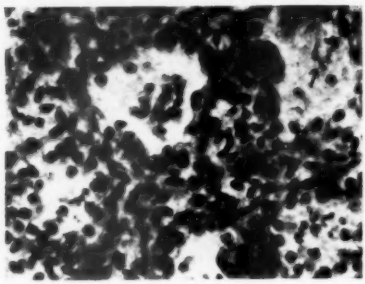


FIG. 13.



FIG. 14.

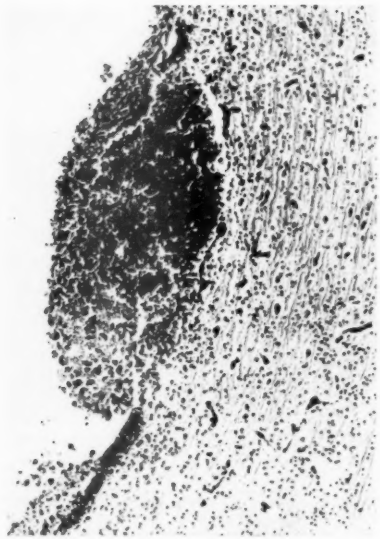


FIG. 15.

FIG. 12.—Pneumonia in a 9 cm. fœtus. This was an ectopic gestation in a fallopian tube, th pneumonia cannot be related to rupture of membranes. × 300.

FIG. 13.—Pneumonia in a 22-week stillborn fœtus. The mother had pyelonephritis with bloo ureas of 305 and 345 mg. %. She made a complete recovery. Coliform bacilli in an alveolus a indicated by the arrow. × 300.

FIG. 14.—Extensive hæmorrhagic lesions in the spinal cord of a full term stillborn anencepha fœtus. × 30.

FIG. 15.—One of many asphyxial cerebral hæmorrhages in a 12 cm. fœtus. All red cells nucleate The macrophage reaction and formation of hæmosiderin shown below the main hæmorrha indicate that it has been present a few days. Pregnancy terminated surgically for maternal toxæn with hypertension. Placenta showed gross appearances of hydatidiform mole. × 75.

G. R. OSBORN

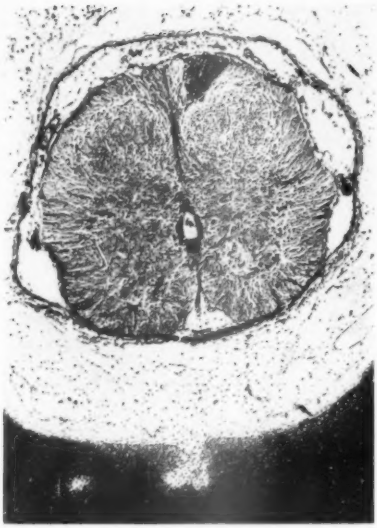


FIG. 16.

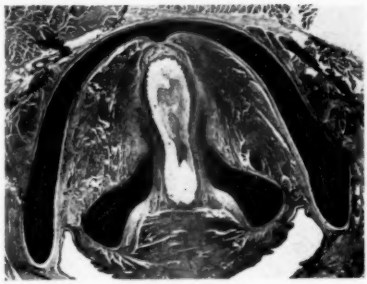


FIG. 17.

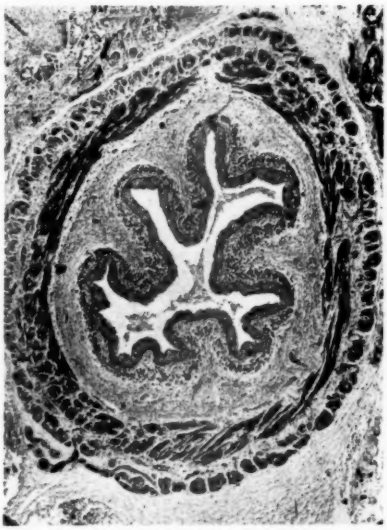


FIG. 19.

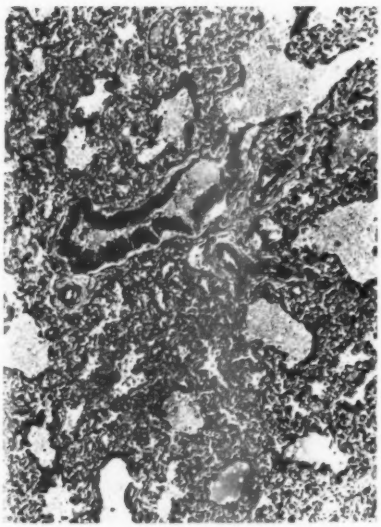


FIG. 18.

FIG. 16.—Hæmorrhage into the posterior columns of the spinal cord of the fœtus described under Fig. 15. All red cells nucleated. Large subpleural asphyxial hæmorrhages also showed nucleated red cells. × 30.

FIG. 17.—Ball-valve obstruction above glottis by inspissated mucus in one of very few stillbirths found with collapsed lungs. A similar plug below the glottis will cause obstructive emphysema in a live birth. Valvular phenomena are also important in the bronchi. × 2.

FIG. 18.—Thick hyaline membrane and gross hæmorrhagic acute pulmonary œdema causing airless lungs in a baby known to have lived 24 hours. Many pathologists have diagnosed such cases as stillbirths. × 150.

FIG. 19.—Normal œsophagus in a 24 cm. fœtus. This is the regular appearance in stillbirths though some show more congestion and a few have asphyxial hæmorrhages, never mucosal ulceration. × 20.

C. R. OSBORN



FIG. 20.



FIG. 21.

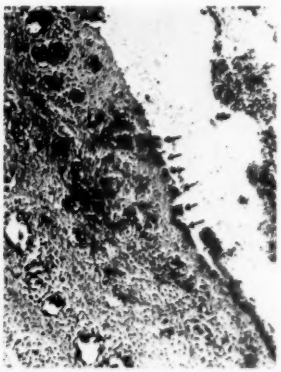


FIG. 22.

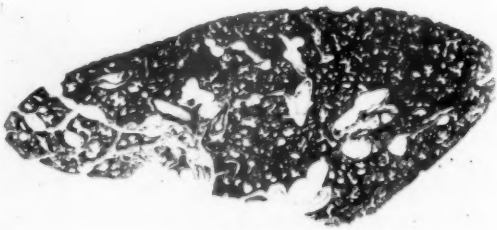


FIG. 23.




FIG. 24.

FIG. 20.—Congestion, hæmorrhages, pressure atrophy and ulceration of epithelium except in a few protected parts. Death at 9 hours. Treated with intragastric oxygen. × 20.

FIG. 21.—Generalized ulceration of the œsophagus with an inflammatory exudate. The baby died at 33 hours after prolonged treatment with intragastric oxygen. There was an extensive hyaline membrane and a cerebral hæmorrhage. × 20.

FIG. 22.—Masses of staphylococci, indicated by arrows, on the ulcerated surface of the œsophagus. The baby died at 7 days and had repeated treatments with intragastric oxygen. × 20.

FIG. 23.—Ballooning and rupture of alveolar ducts, interstitial emphysema and double pneumothorax. Hyaline membrane present. Death 24 hours after delivery by Cæsarean section. × 2.

FIG. 24.—Gross interstitial pulmonary emphysema and double pneumothorax. Asphyxial hæmorrhages on pericardium. Normal delivery. Fœtal distress had been shown by passage of meconium which was later cleared from the air passages. Did not respond to treatment in oxygen tent, etc., but did for a short time to mouth-to-mouth artificial respiration. Full term. Death at 3 hours.

G. R. OSBORN

**Dr. A. E. Claireaux** (London):

During the month of March 1958 a survey was carried out on a national scale of all births during the first week (i.e. March 3–9 inclusive) and in addition, as far as possible, all stillbirths and neonatal deaths were subjected to a full post-mortem examination during the entire month. The data on these cases are still coming in but the results of the survey as they affect one region, namely the South West Metropolitan Regional Hospital Board area, are available. The cases examined in the Western part of the region are excluded and a few cases in the coastal strip of Sussex and Hampshire were examined either at Brighton or Southampton and are also not included in the series. I should like to take this opportunity of thanking all the obstetricians, pædiatricians and pathologists who co-operated in allowing material to be examined at one centre. I am indebted to Dr. R. Osmond of Adelaide for the compilation of the tables.

The results are shown in Table I. There was a total of 107 cases examined at Queen

TABLE I.—COMPARISON OF MARCH 1958 SURVEY and QUEEN CHARLOTTE'S HOSPITAL 1948–1955 SERIES

| Year | Neonatal deaths | Still-births | Total stillbirths and neonatal deaths: Fresh | Macerated | Male | Female | Total |
|---|---|---|---|---|---|---|---|
| March 1958 .. .. | 46 | 61 | 26 | 35 | 64 | 43 | 107 |
| Q.C.H. 1948–1955 series | 410 | 646 | 293 | 353 | 615 | 441 | 1,056 |

Charlotte's Maternity Hospital, the designated Regional Pathology Centre, during the month of March. Of these 61 were stillborn and there were 46 neonatal deaths. It will be seen that the numbers compare very closely with those of a series of 1,056 cases examined at Queen Charlotte's during the years 1948–55. The male/female sex ratio of 1·5 : 1 is maintained and the proportion of stillbirths and neonatal deaths is almost exactly comparable. The latter include infants delivered on District who were not considered when the series was first reported (Claireaux, 1958).

In Table II the presumed cause of death in so far as it is revealed by autopsy is listed. Anoxia is the main cause as far as stillbirths are concerned. The insult is thought to have originated antepartum in 49·2% and intrapartum in 16·4%. Of course all deaths might be attributed in the last resort to anoxia and the term has to be used with some reserve if it is to mean anything at all. The post-mortem diagnosis of anoxia depends on the demonstration of asphyxial petechial hæmorrhages over the thoracic organs or evidence of interstitial or intra-alveolar bleeding in the lungs or excessive aspiration of the contents of the amniotic sac, e.g. liquor amnii or meconium, or both.

TABLE II.—STILLBIRTHS IN MARCH SURVEY

| Cause of death | Total | % |
|---|---|---|
| Antepartum anoxia .. .. .. .. | 30 | 49·2 |
| Intrapartum anoxia .. .. .. .. | 10 | 16·4 |
| Developmental defects .. .. .. .. | 8 | 13·1 |
| Birth trauma .. .. .. .. .. | 5 | 8·2 |
| Antepartum death (placental insufficiency) .. | 4 | 6·6 |
| Antepartum death (cause unknown) .. .. | 3 | 4·9 |
| Hydrops fœtalis .. .. .. .. .. | 1 | 1·6 |
| Total | 61 | 100·0 |

Birth trauma (8·2%) is similar to that in the Queen Charlotte's series of 646 (7·9%) and is almost entirely confined to subdural hæmorrhage, either from tentorial tears or laceration of the great cerebral vein or tear of the falx cerebri. There was one case of a fracture of the spinal column and a massive hæmothorax.

Developmental defects of such severity as to result in stillbirth were unusually frequent (13·1%) as compared with 8·8% in the other series. This is entirely due to the large number of anencephalic fœtuses (6 cases). Preliminary figures suggest that this undue proportion of anencephalus will also be reflected in the national series. This is one of the more striking features of the survey in our investigations to date. The male/female sex ratio was 1 : 1 in our small series which thus does not show the expected preponderance of females among cases of anencephalus.

There were 4 cases of antepartum death which have been attributed to placental insufficiency. In these the placental/fœtal weight ratio was lower than 1 : 7 and in addition, more than half of the placental tissue was infarcted. The placentæ were thus very small and also there was only a small proportion of the placental tissue available for oxygen exchange and nutrition of the fœtus. In the absence of accurate methods for the assessment



FIG. 1.

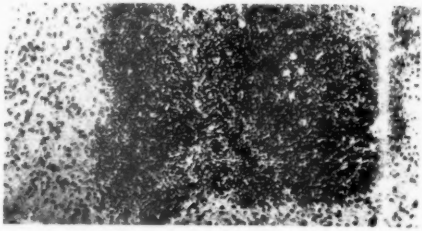


FIG. 2.

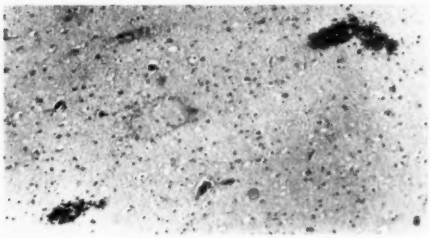


FIG. 3.

FIG. 1.—Brain × 20. Subependymal hæmorrhage in wall of lateral ventricle. Premature infant.

FIG. 2.—Brain × 75. Intracerebral hæmorrhage with destruction of brain tissue. Premature infant.

FIG. 3.—Brain × 75. Perivascular anoxic hæmorrhage in brain substance. Full-term infant.

of normal placental function the diagnosis of placental insufficiency has been reserved for the few cases where there was an extremely small amount of functioning placental tissue available.

In 3 cases (4·9%) antepartum death had occurred and no demonstrable lesion was found at autopsy. There was 1 case of hydrops due to Rhesus iso-immunization.

The neonatal deaths (46) are shown in Table III. In the right-hand columns the percentage

TABLE III.—COMPARISON OF CAUSES OF NEONATAL DEATH IN MARCH SURVEY AND UNIVERSITY COLLEGE HOSPITAL 1956 SERIES

| March Survey 1958 Cause of death | Total | % | Total | % | U.C.H. 1956 Cause of death |
|---|---|---|---|---|---|
| Atelectasis | 10 | 21·7 | 59 | 26·7 | Pulmonary syndrome of newborn |
| Intrapulmonary hæmorrhage | 5 | 10·9 | | | |
| Birth trauma | 9 | 19·6 | 40 | 18·1 | Birth trauma |
| Developmental defects | 9 | 19·6 | 33 | 14·9 | Congenital malformation |
| Intracranial haemorrhage (other than subdural) | 4 | 8·7 | 21 | 9·5 | Intraventricular hæmorrhage |
| Infection | 3 | 6·5 | 27 | 12·2 | Pneumonia |
| Intrapartum anoxia | 2 | 4·3 | 11 | 5·0 | Intrapartum asphyxia |
| Previability | 2 | 4·3 | 11 | 5·0 | Previability |
| Hæmolytic disease | 1 | 2·2 | 7 | 3·2 | Erythroblastosis |
| Emphysema | 1 | 2·2 | 12 | 5·4 | Miscellaneous |
| Total | 46 | 100·0 | 221 | 100·0 | |

distribution of the series of 221 consecutive necropsies on neonatal deaths reported by Bound *et al.* (1956) is included for comparison. The latter used the term "pulmonary syndrome of the newborn" to include cases of atelectasis associated with one or more of the following: (1) hyaline membrane, (2) intra-alveolar hæmorrhage, (3) pulmonary œdema. I have kept the cases of intrapulmonary hæmorrhage separate for a number of reasons but otherwise the series is comparable. There were only 3 deaths occurring over seven days after delivery in the survey material. One case died of meningitis and is included with the infections. The other 2 cases were severe congenital malformations of the heart and this supports the opinion I have held for some time that neonatal deaths from the 2nd to the 4th week after delivery are usually the result of a congenital malformation or of infection.

Atelectasis was found in 10 cases (21·7%). It was associated with hyaline membrane formation in 6 (60%) which compares with 73% in the University College Hospital series. 8 of the 10 cases of atelectasis occurred in infants under 2,500 grams birth weight.

Birth trauma (9 cases) accounted for 19·6% of the neonatal deaths. This figure is co-

parable with that of the U.C.H. series but, as will be seen, is more than double that of the 1948–55 series at Queen Charlotte's Hospital. Death resulted from severe subdural hæmorrhage in all cases. The underlying lesion again was a tentorial tear, tear of the falx or a laceration of the great cerebral vein. It is unfortunately not yet possible to relate the incidence of birth trauma to the total deliveries during the period under observation but it is almost certainly in excess of the figure of 0·5/1,000 births (3% of stillbirths and neonatal deaths) claimed by Potter (1952) at the Chicago Lying-In Hospital. It would seem that the figure we have obtained is still much too high and that the number of deaths from birth trauma could still be reduced in our region.

Developmental defects (9 cases) were responsible for 19·6% of deaths and, if the 2 infants with congenital heart malformations who died after seven days are excluded, the figure becomes 15·2%, which is comparable with the U.C.H. series.

There were only 3 cases of infection, 2 examples of pneumonia and 1 of meningitis. The organisms responsible were *B. proteus*, *B. proteus* and coliforms, and a beta hæmolytic streptococcus, not Lancefield Group A, B, C, D, or G in the meningitis case.

Intrapartum anoxia caused 2 deaths. The infants died very shortly after birth and typical anoxic changes were present in the thoracic organs.

In 2 cases the infant was judged to be previable and had a birth weight of under 1,000 grams with no anatomical lesion to account for death on post-mortem examination. Prematurity, i.e. birth weight of 2,500 grams or less, was an important contributory factor among the neonatal deaths. Of the 46 infants 28 (60%) were premature.

There was one case of emphysema and pneumothorax and one case of hæmolytic disease.

Intracranial hæmorrhage other than subdural hæmorrhage accounted for 4 of the deaths (8·7%). The hæmorrhage in this instance was subarachnoid and intraventricular in distribution and not into the subdural space. All 4 cases were infants of under 2,500 grams birth weight. Severe intraventricular hæmorrhage is of anoxic rather than of traumatic origin. It usually arises from the rupture of a subependymal hæmorrhage in the wall of one of the lateral ventricles (Fig. 1). These hæmorrhages arise in the subependymal spongioblastic layer and are caused by bleeding from the venæ terminales. The spongioblastic laver of the developing brain in the premature infant offers little resistance to the spread of blood from a perivascular hæmorrhage. A subependymal blood blister is formed and this eventually may rupture into the ventricle. The blood then spreads through the ventricular system, out into the basal cisterns and into the subarachnoid space over the hemispheres. A number of cases of intraventricular hæmorrhage are associated with an intracerebral hæmorrhage, the blood bursting outwards from the lateral ventricle into the brain parenchyma (Fig. 2). The subependymal hæmorrhages are of anoxic origin but the exact time of their occurrence is uncertain. In some cases they probably originate during labour and they are then examples of intrapartum anoxia. The lesion is occasionally seen in a stillborn fœtus. Others are not infrequently associated with atelectasis and hyaline membrane formation and thus with post-partum anoxic changes. In still another group the subependymal hæmorrhage may arise during labour and respiratory difficulty after birth may lead to the rupture of the blister into the ventricle. For these reasons the cases have been classified on their own. By contrast, in the mature infant perivascular anoxic hæmorrhages are sharply circumscribed and seldom coalesce to form macroscopic hæmorrhagic areas (Fig. 3).

In Table IV the neonatal deaths occurring from 1948–55 at Queen Charlotte's Hospital are shown in detail. This is a series from a purely hospital population. Again disorders of the lungs account for 38·3% of the total and form the largest single group. Birth trauma (8·3%) is considerably less prominent and congenital abnormalities (11·9%) are also proportionately fewer. Infection was the cause of death in 43 cases (10·5%) but it must be remembered that some of these cases occurred some time ago when infection was probably of even greater import than it is today. Hæmolytic disease is represented by 35 cases (8·5%) and 15 of these infants died with kernicterus. It is to be expected that a larger proportion of hæmolytic disease cases would occur at Queen Charlotte's Maternity Hospital than in the region as a whole, as the hospital tends to attract the mother with antibodies in her serum. Kernicterus, too, is a complication of hæmolytic disease which has been almost eliminated in the past few years by modern methods of exchange transfusion therapy and serum bilirubin control. Thus the proportion of deaths from hæmolytic disease in a future eight-year sample would be very much smaller. The same applies to kernicterus of prematurity. There was no example of this in the March series. Intraventricular hæmorrhage took a toll of 33 cases (8·1%) and the incidence is the same as in the March series. Intrapartum anoxia 21 cases (5·1%) also accounted for a similar proportion of the cases in each series. There were 12 previable infants (3%) and 19 cases in the miscellaneous group. This included such conditions as meconium peritonitis (3 cases), intraperitoneal hæmorrhage (3 cases) and suprarenal hæmorrhage (2 cases).

TABLE IV.—NEONATAL DEATHS IN QUEEN CHARLOTTE'S HOSPITAL SERIES 1948–1955

| Cause of death | Total | % |
|---|---|---|
| Atelectasis | 131 | 32·0 |
| Intrapulmonary hæmorrhage | 26 | 6·3 |
| Developmental defects | 49 | 11·9 |
| Infection | 43 | 10·5 |
| Hæmolytic disease | 35 | 8·5 |
| Birth trauma | 34 | 8·3 |
| Intracranial hæmorrhage (other than subdural) | 33 | 8·1 |
| Intrapartum anoxia | 21 | 5·1 |
| Previability | 12 | 3·0 |
| Kernicterus of prematurity | 7 | 1·7 |
| Miscellaneous | 19 | 4·6 |
| Total | 410 | 100·0 |

*Importance of intracranial lesions.*—Although intracranial lesions are somewhat less frequent as a cause of death than are disorders of the lungs among stillbirths and newborn infants, they form an important group in neonatal pathology. From Table V it will be

TABLE V.—INCIDENCE OF CRANIAL LESIONS (STILLBIRTHS AND NEONATAL DEATHS) IN INFANTS WEIGHING OVER 500 GRAMS. 1948–1955

(These figures include those cases where the cranial lesion was an associated post-mortem finding.)

| Nature of lesion | Stillbirths | Neonatal deaths | Total |
|---|---|---|---|
| Intraventricular hæmorrhage | 18 | 47 | 65 |
| Subdural hæmorrhage | 68 | 49 | 117 |
| Intracerebral hæmorrhage | 0 | 8 | 8 |
| Subarachnoid hæmorrhage | 3 | 7 | 10 |
| Subependymal hæmorrhage | 0 | 4 | 4 |
| Intracerebral petechiæ | 0 | 2 | 2 |
| Congenital abnormalities | 56 | 23 | 79 |
| Kernicterus (hæmolytic disease) | 0 | 15 | 15 |
| Kernicterus (premature infants) | 0 | 7 | 7 |
| Fracture of skull | 2 | 1 | 3 |
| Meningitis | 0 | 2 | 2 |
| Cerebral abscess | 0 | 1 | 1 |
| Total | 147 | 166 | 313 |

Total number of stillbirths and neonatal deaths .. 1,056

" " " neonatal deaths .. 410

seen that out of a total of 1,056 necropsies there were 313 cases with some intracranial lesion although this was not necessarily itself responsible for the stillbirth or neonatal death.

Hæmorrhage is the main lesion. This may be subdural in situation (117 cases) and associated with birth trauma, intraventricular and subarachnoid (75 cases) associated with anoxia, or intracerebral (8 cases) where the ætiological factor may be anoxia or vascular thrombosis.

There were also 4 cases of subependymal hæmorrhage where the subependymal blister had remained intact and had not burst the lining of the ventricle. In 2 cases microscopic perivascular hæmorrhages were found in the brain on histological examination. These occurred in full-term infants and are probably more frequent than the table would suggest but detailed histological examination of the brain in cases of anoxia has only been undertaken comparatively recently.

Kernicterus accounted for 22 cases, 15 in hæmolytic disease and 7 among premature infants. With modern methods of exchange transfusion therapy and daily estimation of serum bilirubin levels this lesion should largely disappear. Since 1955 I have only seen 1 case of kernicterus at Queen Charlotte's Hospital; this occurred in a very small infant of under 2 lb. weight whose condition was such that exchange transfusion could not be contemplated. We have not observed kernicterus as a complication of hæmolytic disease in any case delivered in Queen Charlotte's since 1955.

Severe birth trauma which is sufficient to cause a fracture of the skull is a rare event in modern obstetrics. There were only 3 such examples in this series. The most recent was

in an unbooked case admitted in the second stage of labour. The pelvis was inadequate and although delivery was effected by forceps the squamous and basal portions of the occipital bone became separated with a resulting devastating hæmorrhage from torn venous sinuses.

Infection nowadays plays a very small part in intracranial pathology in the newborn. There was 1 case of abscess formation and only 2 cases of meningitis in the eight years covered by the series.

*Congenital malformations* (Table VI).—There were 27 cases of anencephalus (8 male and 19 female), the male/female ratio was 1 : 2·4. Hydrocephalus accounted for 37 cases. In 16 there was no other associated intracranial abnormality but in 21 there was in addition a malformation of the brain such as an Arnold-Chiari defect. There were 9 cases of hydrocephalus associated with spina bifida defect but not with an Arnold-Chiari malformation. The latter is usually found in association with a meningomyelocele as well as a spina bifida. The spinal lesion is usually in the lumbar region. If the spina bifida defect is not accompanied by a meningomyelocele the Arnold-Chiari malformation is usually also absent. Together hydrocephalus and anencephalus are responsible for 81% of the central nervous system abnormalities. Other defects such as encephalocele (9 cases) are rather less common and such conditions as iniencephalus and hydranencephalus are excessively rare.

TABLE VI.—CONGENITAL ABNORMALITIES OF THE BRAIN (STILLBIRTHS AND NEONATAL DEATHS) INFANTS WEIGHING OVER 500 GRAMS.

1948–1955

| Nature of deformity | No. of cases |
|---|---|
| Anencephalus | 27 |
| Hydrocephalus (and no other intracranial abnormalities) | 16* |
| Hydrocephalus (and other major intracranial defects—e.g. Arnold-Chiari malformation, etc.) | 21 |
| Iniencephalus | 2 |
| Encephalocele | 9 |
| Microcephalus | 1 |
| Hydranencephalus | 1 |
| Others | 2 |
| Total | 79 |

*Including 9 cases with associated spina bifida.

*Conclusions.*—It is possible from this brief survey to arrive at only a few rather tentative conclusions.

(1) It would seem from the sample of cases from the Perinatal Mortality Survey so far examined that the general distribution as to sex, stillbirth and neonatal death is similar to that in a much larger sample from a purely hospital population.

(2) As in most other series anoxia accounts for most of the losses among stillbirths and some disorder of respiration is responsible for the majority of the neonatal deaths. Prematurity is also a most important factor.

(3) Birth trauma still plays an important part in the causation of stillbirth and neonatal death. The figures so far obtained during the survey would seem to suggest that the loss from this cause could be still further reduced.

(4) The main difference between the two groups of cases reviewed lies in the rather large number of congenital abnormalities among the Survey material and the prominence of hæmolytic disease of the newborn among the hospital cases. The latter is explained by the fact that certain hospitals may well attract this type of patient and their experience is not that of the population at large. The relatively low incidence of severe congenital malformations in the hospital group is not fully understood.

(5) Anencephalus, hydrocephalus and congenital malformations of the heart account for most of the severe defects among stillbirth and neonatal deaths.

(6) The incidence of anencephalus in the Survey group is surprisingly high and it is believed that this will be reflected in the national figures when these are complete.

## REFERENCES

BOUND, J. P., BUTLER, N. R., and SPECTOR, W. G. (1956) *Brit. med. J.*, ii, 1191.
CLAIREAUX, A. E. (1958) In: Modern Trends in Pædiatrics (2nd ser.). Edited by A. Holzel and J. P. M. Tizard. London; p. 52.
POTTER, E. L. (1952) Pathology of the Fetus and Newborn. Chicago.

**Dr. Jean M. Smellie** (London):

This contribution to the discussion will be concerned with the clinical aspects of figures derived from the University College Hospital Obstetric Hospital.

Table I shows the causes of neonatal deaths in University College Hospital over the

TABLE I

| Cause of death | Premature | Full-time | % |
|---|---|---|---|
| Pulmonary syndrome of the newborn | 53 | 6 | 26·7 |
| Birth trauma | 25 | 15 | 18·1 |
| Congenital malformations | 15 | 18 | 14·9 |
| Pneumonia | 16 | 11 | 12·2 |
| Intraventricular hæmorrhage | 20 | 1 | 9·5 |
| Miscellaneous | 9 | 3 | 5·4 |
| Previability | 11 | — | 5·0 |
| Intrapartum asphyxia | 5 | 6 | 5·0 |
| Erythroblastosis fœtalis | 3 | 4 | 3·2 |

period 1948–55 in a series of 221 autopsies analysed by Bound *et al.* (1956). Pulmonary syndrome of the newborn heads the list with a great preponderance among premature infants. Two-thirds of all these neonatal deaths were premature, but the figures also include deaths in a small number of premature infants admitted from outside. The decline in neonatal deaths over the past twenty years has resulted from improved obstetric and neonatal care. Few large babies die from birth trauma, infection and hæmolytic disease of the newborn. This has resulted in a proportionate rise of deaths of premature infants.

Fig. 1 shows the neonatal death rate per 1,000 live births in University College Hospital

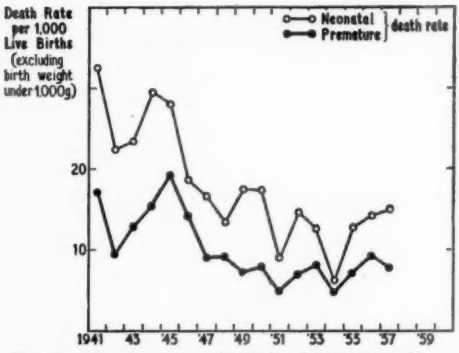



FIG. 1.—Death rate per 1,000 live births (excluding birth weight under 1,000 grams.)

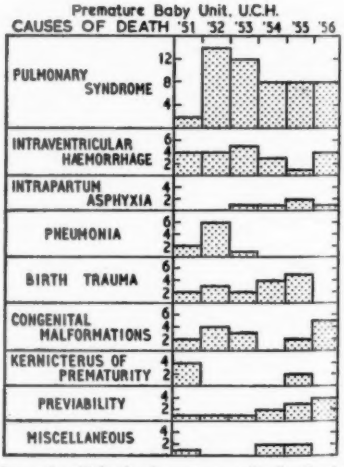



FIG. 2.—Principal causes of death in absolute numbers in premature infants.

excluding infants weighing less than 1,000 grams. The lower line indicates premature deaths per 1,000 live births also excluding those under 1,000 grams. (Accurate figures for these were not available before 1950.) In 1942, prematurity was the cause of 42% of the deaths, while between 1954 and 1957 it has been associated with 60–80% of our neonatal deaths. Prematurity, always a prominent factor in neonatal deaths, is increasing in importance.

There has been some change over the years in the causes of death in premature infants. Fig. 2 shows in absolute numbers the principal cause of death in premature infants in University College Hospital. Total numbers of premature infants nursed in the Unit annually have remained fairly constant and about a quarter were admitted from outside. Current trends are shown. Kernicterus should not now occur. Pneumonia has been eliminated by the judicious use of prophylactic antibiotics. Previability is on the increase. Intraventricular hæmorrhage probably asphyxial in origin takes a steady toll and "pulmonary syndrome" heads the list.

Pulmonary syndrome of the newborn has been defined by Bound *et al.* (1956) as a condition associated with neonatal death in the first week of life, characterized by resorption atelectasis together with one or more of the following features: hyaline membrane, pulmonary hæmorrhage and pulmonary œdema. The great majority are premature and the other main association is with Cæsarean section.

In 1957, pulmonary syndrome of the newborn was primarily responsible for half of the neonatal deaths in premature infants and pulmonary pathology was found in 72% of premature infants at autopsy, at University College Hospital.

Clinically, infants with this syndrome show two groups of symptoms, respiratory and cerebral. They may be born in good or poor condition and develop signs of respiratory distress usually during the first twelve to twenty-four hours of life, with lower rib or sternal recession and expiratory grunt. Respiratory movement is shallow, may be irregular in rhythm and become rapid, and apnœic attacks may occur. Some have enlarged livers, many are œdematous and death may occur a few hours to several days after birth. Recovery, when it occurs, is likely to be complete.

Cerebral symptoms may develop twelve to thirty-six hours after birth, usually after a period of respiratory difficulty (and similar symptoms are seen in some infants born at or after term who have been anoxic during or after delivery). The fontanelle becomes full, the liver enlarged, the infant restless with an alteration in limb tone and there may be vomiting or convulsions.

The first group of symptoms may be difficult to differentiate from pneumonia and certain congenital malformations such as diaphragmatic hernia; the second group may be indistinguishable from intracranial birth trauma. In fact, in 63% of fatal cases showing cerebral symptoms pulmonary pathology alone was found (Bound *et al.*, 1956).

The problem has many facets, but we were impressed by the resemblance of some infants with this condition to babies with congestive cardiac failure—the enlarged liver, the grunting respirations and œdema. After remarkable success with intravenous Digoxin in one such infant we set out to show that babies with respiratory difficulty died of anoxic cardiac failure and that treatment with digitalis would be beneficial.

Our first investigation was of mean venous pressure measured through the umbilical vein (Bonham Carter *et al.*, 1956). Briefly recapitulating our results, we found a normal range of venous pressure of 0·2–5·0 cm. of water uninfluenced by birth weight or age at recording.

Fig. 3 shows our results in 32 infants with respiratory difficulty. In 25 where records

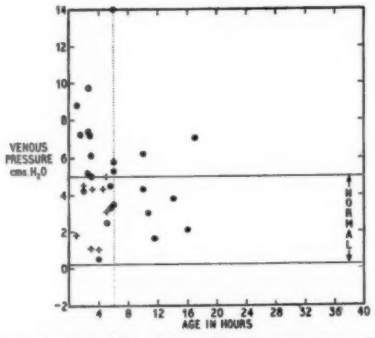



FIG. 3.—Venous pressures in 32 infants with delay in expansion of lungs (25 infants aged 6 hours or less, birth weights 2 lb. to 10 lb.). + = fatal cases. ● = survivors.

were made during the first six hours, all fatal cases had a mean venous pressure in the normal range and half of the survivors had a raised pressure. This appeared to reverse our hypothesis. A raised venous pressure appeared beneficial to infants with respiratory difficulty. This raised the problem of expansion of neonatal lungs.

It seems unlikely that a pressure difference between atmosphere and pleura is the only factor. Do the infants who die have a normal venous pressure because, as Lendrum (1955) suggests, the mechanical changes in the circulation produce a left-sided heart strain, pulmonary œdema and failure to absorb liquor from the lungs? It is also possible that lungs expand on the pulmonary vascular bed, as on erectile tissue, as suggested by Jäykkä (1957) and amplified by Bonham Carter (1957). Anoxia raises the pulmonary vascular

resistance as shown by Rowe and James (1957) and an increase in the right heart output dependent upon a raised venous pressure may then be necessary to overcome the pulmonary vascular resistance.

If we accept a raised venous pressure as beneficial what are the factors likely to influence it? The most obvious one is the blood volume. Gunther (1957) has shown by weighing methods that a baby may alter his blood volume by about 40% according to the position and time of tying the cord. For example, one of her recordings showed the effect of raising a baby above the level of the placenta and of subsequent lowering, within the first five minutes of life and after cessation of cord pulsation. The former produced a loss of 40 grams which was followed by a gain of 80 grams, representing a variation of about one-fifth of the infant's blood volume. The infants likely to be deprived of such a placental transfusion are those born by Cæsarean section where the baby is held above the placenta and the cord clamped immediately; and premature babies who are going to be removed rapidly to a warm cot, and in whom a small depletion of blood will make a disproportionate difference.

Another group of infants with low blood volume at birth is that described by Butler and Martin (1954) and Neligan and Russell (1954) where the placenta is incised during Cæsarean section for anterior placenta prævia. In one case where transfusion was delayed, death ensued, a hyaline membrane being found at autopsy.

Our only neonatal death from hæmolytic disease since 1950, excluding four living cases of hydrops fœtalis, was in an infant delivered by Cæsarean section at thirty-four weeks where the venous pressure was normal at commencement of exchange transfusion and death at eight hours was due to pulmonary syndrome. He was left with a small deficit of blood at the conclusion of the exchange and was the only one of 6, where a record was made, with a normal venous pressure initially.

We set out to prove that babies dying from the pulmonary syndrome of the newborn did so from cardiac failure and we showed unexpectedly that a raised venous pressure in the first hours of life was beneficial. Now we offer facts which suggest that some infants developing pulmonary syndrome have been deprived of blood as a result of their premature or Cæsarean delivery. Prematurity is mainly responsible for the hard core of neonatal deaths and the best solution would be a reduction of the incidence of prematurity. Until that time, it seems desirable to avoid Cæsarean section in premature delivery where possible and to hold the baby below the level of the placenta for several minutes, before tying the cord. This is not the whole solution but we believe that there is a circulatory factor which contributes to the problem.

## REFERENCES


Bonham Carter, R. E. (1957) *Lancet*, i, 1292.

——, Bound, J. P., and Smellie, J. M. (1956) *Lancet*, ii, 1320.

Bound, J. P., Butler, N. R., and Spector, W. G. (1956) *Brit. med. J.*, ii, 1191, 1260.

Butler, N. R., and Martin, J. D. (1954) *Brit. med. J.*, ii, 1455.

Gunther, M. (1957) *Lancet*, i, 1277.

Jäykkä, S. (1957) *Acta pædiat. Stockh.*, **46**, suppl. 112.

Lendrum, F. C. (1955) *J. Pediat.*, **47**, 149.

Neligan, G. A., and Russell, J. K. (1954) *J. Obstet. Gynæc., Brit. Emp.*, **61**, 206.

Rowe, R. D., and James, L. S. (1957) *J. Pediat.*, **51**, 1.


[*July* 15, 1958]

## Special Meeting

**Professor Naguib Mahfouz,** M.Ch.Cairo, F.R.C.P.London, Hon. F.R.C.S.England, Hon. F.R.C.O.G., demonstrated films of his operative technique for vesicovaginal fistulæ and rectovaginal fistulæ.

# Section of Neurology

President—W. RITCHIE RUSSELL, C.B.E., M.D., D.Sc., F.R.C.P.

[*March* 27, 1958]

## DISCUSSION ON SOME CLINICAL, GENETIC AND BIOCHEMICAL ASPECTS OF METABOLIC DISORDERS OF THE NERVOUS SYSTEM

**Dr. W. B. Matthews** (Derby):

*Metabolic Disease of the Nervous System: Clinical Aspects*

*Inborn Errors of Metabolism*

It is not possible to discuss clinical aspects of inborn errors of metabolism without a brief incursion into biochemistry and genetics. Dent (1957*a*) has stated that if we believe in the genetic theory of inheritance it is not permissible to speak of inborn errors of metabolism of the nervous system, or of the renal tubule or of any other organ. The abnormal gene is universally distributed in the somatic cells. For the clinician this emphasizes the importance of recording associated abnormalities in inherited nervous disease. Numerous examples come to mind; it was pigmentation of the skin that first led to the suspicion of metallic poisoning in Wilson's disease. The recent report on the association of ichthyosis, mental defect and spastic paralysis (Sjögren and Larsson, 1957) shows that clinical observation may still have much to contribute.

There is general agreement that metabolic errors are the expression of defective or abnormal enzyme action. Much of the basis for this belief rests on elegant experiments on unicellular organisms. As far as I am able to understand this work it seems to contain certain valuable ideas for the clinician. It is probable that although the abnormal gene may be present in every cell the resulting metabolic error is only potentially present. It has been shown that in certain instances not only the action, but even the production of a genetically-induced enzyme may be controlled by the environment. A second significant finding is that enzyme abnormalities are not necessarily absolute; an enzyme may be reduced in quantity but not completely absent (Davis, 1954). If these findings can be applied to human disease they are of some importance as, at first sight, a disease due to an intracellular enzyme defect is not a promising therapeutic subject. It is through the environment that we can hope to exert any influence and there is strong evidence that in many instances it is environmental factors that are responsible for the production of symptoms. A puzzling feature of certain of these diseases is that, in spite of a presumably constant metabolic defect, symptoms are often episodic and sometimes very acute. Another feature is the great variation of clinical response to an apparently stereotyped biochemical disorder. Even in a single family great variation may occur and between families there are often wide differences in the age of onset and severity of symptoms. The interaction of the genetic defect, which may itself perhaps vary in degree from case to case, and the environment, is of vital importance.

It may one day be possible to classify inborn errors according to the enzyme at fault and to describe the manner in which the nervous system is affected. We are very far from this at present and even in apparently simple examples there is no agreement. In the condition of congenital methæmoglobinæmia a varying proportion of the hæmoglobin is unable to transport oxygen. The disease is characterized by fluctuating cyanosis and, in some instances, by mental defect and motor retardation. It is tempting to attribute the mental defect to anoxia, but here we meet a recurring theme in writing on hereditary disease, as it has been suggested that the cerebral damage is not causally connected with the metabolic defect but is separately inherited (Worster-Drought *et al.*, 1953). There is recent evidence that this may not be so. Dine (1956) reported a family in which the elder child was diagnosed

and treated with reducing agents at the age of 18 days and grew up retarded. The second child was treated at the age of 4 hours and has so far developed normally. Dine plausibly suggests that anoxia in the vulnerable neonatal period may be responsible for cerebral damage, when this is present. This introduces another complicating factor, the suggestion that the biochemical defect may only affect the nervous system at certain stages of its development.

The episodic nature of the symptoms found in certain metabolic errors is well shown by the recent description of Hartnup disease by Baron and others (1956). The symptoms are certainly suggestive of pellagra, although not thought to be entirely typical, and the rash and ataxia appear in acute episodes. Dent (1957*b*) has reported dementia in the older members of the Hartnup family, so that more permanent effects also seem to be produced. Dent considered the acute attacks were probably the result of environmental factors, but was not able to identify these, and could not be certain whether altering the environment by adding excess nicotinamide to the diet produced any therapeutic benefit.

This episodic clinical picture is shown even more clearly by acute intermittent porphyria and here some at least of the environmental factors are known. Garcin and Lapresle (1950) in their review of the clinical features of porphyria emphasize that *chronic* neurological and psychiatric disease does not occur. Certainly I have found that the routine testing for porphobilinogen in cases of organic dementia and chronic polyneuritis has been unrewarding. I have seen 2 patients who were incapacitated by a mild dementia following an acute attack, but, in general, the problem is that of prevention, detection and treatment of the acute attack. Dean and Barnes (1958) state that in the form of acute porphyria found in South Africa acute attacks are *always* precipitated by drugs, notably barbiturates. This form of porphyria is clinically and biochemically distinct from that usually found in this country and here it is certainly not always possible to incriminate drugs, but the exacerbation following heavy sedation with barbiturates when the diagnosis has been missed is only too well known. The full combination of abdominal colic, paralysis, fits and psychiatric symptoms is very characteristic, but the incomplete syndrome may be very easy to miss. My most recent case presented with a painless hæmatemesis followed by death within thirty-six hours. Detection of the symptomless affected relatives is important so that they can be protected from known environmental risks and here the Watson-Schwartz test for porphobilinogen (Watson and Schwartz, 1941) should not be relied on as it may be negative in patients who have not had an acute attack. Treatment of the attack has been based on supportive measures which may be life saving, but no rational attack on the biochemical disorder has been developed. There have been recent claims that BAL produces good clinical results, but the work requires confirmation and closer chemical control (Peters *et al.*, 1957).

An episodic history is, of course, typical of familial periodic paralysis. I am not qualified to comment on the recent advances in understanding this disease or group of diseases reported by Conn and others (1957). I mention it as an example of a condition where symptoms can be induced by changes in environment, either natural, such as a carbohydrate meal or even sleep, or artificial, such as glucose and insulin combined. Attacks can be prevented by the radical change in environment of a very low sodium diet.

A remittent history is not, of course, found in all inborn errors of metabolism. In certain instances the known environmental factor is constant daily exposure to an item of the normal diet that the patient is unable to metabolize normally. In galactosæmia there is a block in the metabolism of lactose leading to accumulation of metabolites in front of the block. Symptoms usually occur very early with intolerance to milk, vomiting and later mental defect and cataract. It is seldom likely to be seen by neurologists at this stage, but unsuspected cases may be found associated with mental defect in older children (Bergren *et al.*, 1958). There is again controversy about the relationship of the mental defect to the metabolic disorder. It is now possible, however, to establish the diagnosis in suspected cases by examination of the cord blood and to ensure that the child is never exposed to the noxious environment. The subsequent development of such children should settle the disagreement (Schwartz *et al.*, 1958).

Phenylketonuria is another example where the known environmental factor is exposure to a normal dietary constituent and, as might be expected, the disease is not characterized by acute attacks and remissions. The clinical picture is well known: relative lack of pigment, dementia and often epilepsy and evidence of injury to the basal ganglia. Although the great majority of cases are of very low intelligence, normal or almost normal intelligence may rarely be found (Coates *et al.*, 1957; Hsia *et al.*, 1957). This fact is of greater importance than its rarity would suggest as it raises the question of the cause of this great variation of clinical response. In this disease it is known that the metabolic defect can exist in an incomplete form, as clinically normal heterozygotes can be detected by chemical means (Hsia *et al.*, 1956). In affected homozygotes, however, no marked variation in the biochemical defect has been detected, even in cases with relatively normal intelligence

(Hsia *et al.*, 1957). Variations in the degree of genetic defect, which had seemed to me to be a possible explanation, do not appear to be significant and it is difficult to believe that exposure to phenylalanine can be very different from case to case. Unknown influences seem to be at work and, if treatment is to be fully effective, it is important to discover what they are. Determined efforts are being made to influence the disease by withdrawing phenylalanine from the environment. Recent reports suggest that if the environment can be controlled the genetic defect may even be harmless (Bickel *et al.*, 1954; Woolf *et al.*, 1958).

Much work has recently been done on the metabolic defect in Wilson's disease and I do not propose to discuss the chemical theories in any detail. The environmental factor appears to be a continuous one, namely that the normal diet contains more copper than the body requires. The nature of the genetic metabolic defect is still controversial, but most workers believe that the normal, but unknown, mechanisms preventing the absorption of unwanted copper are defective. It seems unlikely that these two factors vary greatly from day to day and yet acute clinical episodes are not infrequent. I may illustrate this by an example of a little-known clinical feature, hæmolytic anæmia. A girl of 6 was originally admitted to Burton General Infirmary under Dr. R. D. C. Johnstone, to whom I am indebted for the original notes. She had suffered from an attack of jaundice followed by ascites. When admitted the jaundice had almost cleared, but then returned suddenly accompanied by a severe fall in the hæmoglobin (Fig. 1). Recovery from the jaundice coincided with a rise in hæmoglobin. When I saw her three years later she had cirrhosis of the liver and corneal rings, but no neurological signs. This anæmia seems to parallel the hæmolytic crises that occur in sheep receiving too much copper in their diet (Marston, 1952). In these animals copper steadily accumulates in the liver and then, without any known environmental change, a hæmolytic crisis occurs accompanied by a rise in the blood copper. I do not know of any case of Wilson's disease diagnosed during a hæmolytic crisis, as they do not seem to occur late in the disease. The state of the blood copper would be of great interest and, in the present context, the anæmia illustrates a mechanism whereby a constant metabolic defect can produce an acute illness.

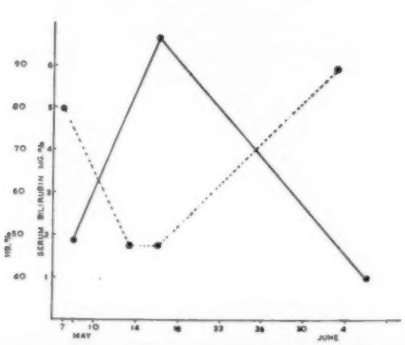



FIG. 1.—Hæmolytic crisis in Wilson's disease. Dotted line: hæmoglobin. Solid line: serum bilirubin.

In this disease an enzyme, cæruloplasmin, has positively been identified as deficient, but unfortunately the function of the enzyme is unknown. It has, however, led to a fundamentally different attempt at treatment of a metabolic error. Bickel and others (1956) have been able to raise the plasma level of cæruloplasmin to normal by injecting the substance. They have not so far been able to report any clinical benefit and the crucial experiment of determining whether absorption of copper is restored to normal does not appear to have been carried out. Treatment has otherwise been concentrated on removing excess copper from the body or on altering the environment by rendering the alimentary copper unabsorbable. Anyone with experience of treating children with BAL will welcome Walshe's (1956) discovery of a chemically effective oral agent, penicillamine. In my experience BAL has been disappointing in children and it requires a hard-hearted physician to persist with regularly repeated courses.

The clinical features are well known and often described. It is therefore surprising that in 5 cases the original hospital diagnoses were juvenile cirrhosis, adolescent scoliosis, schizophrenia, malignant hysteria and excessive maternal solicitude. The temptation to

ascribe peculiar movements to hysteria is often powerful, but is usually worth resisting. A further clinical point is the close resemblance between the clinical and pathological features of the more chronic forms of Wilson's disease and those of cerebral disease secondary to cirrhosis. This resemblance is so close as to have led so eminent an authority as Greenfield (1954) to doubt the specificity of Wilson's disease. There seems to be no doubt about the specificity of the metabolic defect, but our ideas of causation of symptoms may yet require revision.

I must omit certain important groups of diseases, largely because of ignorance. Advances in the understanding of the lipidoses have been limited by the relative ignorance of intermediate lipid metabolism in the brain. Progress is likely to accelerate, both in the discovery of "new" diseases and in elucidation of old enemies. Allan and others (1958) have described a family with convulsions, dementia and an obscure amino-aciduria. Dr. J. H. D. Millar has allowed me to mention that he has found a suggestion of a metabolic disorder in familial myoclonic epilepsy. I recently described a metabolic abnormality in a case of familial calcification of the basal ganglia with normal blood chemistry (Matthews, 1957). Dent has expressed the view that all genetically induced defects are the result of biochemical disorders. If so, such diseases as Huntington's chorea and muscular dystrophy present a formidable challenge.

*Diabetic Amyotrophy*

I would like now to speak briefly about one aspect of carbohydrate metabolism. Garland and Taverner in 1953 drew attention to a purely motor disturbance associated with diabetes. Briefly this is characterized by asymmetrical weakness, usually of the legs, with loss of reflexes, frequently with pain and very seldom with fasciculation. The prognosis is ultimately good although recovery may be long delayed. In a number of instances extensor plantar reflexes had been found and the condition was labelled "diabetic myelopathy". This has been amended to the less committal term of "diabetic amyotrophy" (Garland, 1955). No examination of the spinal cord has been reported.

An example of this condition was admitted to Dulwich Hospital under Dr. S. Nevin when I was working at King's College Hospital. I am indebted to Dr. Nevin for permission to refer to this case, which it is hoped to publish in full. A man of 52 had a five months' history of pain and progressive asymmetrical weakness of the legs, but no diabetic symptoms. He was grossly overweight and had marked weakness of all movements at hip and knee joints, absent ankle-jerks, flexor plantar responses and no sensory loss. The urine contained much sugar, a random blood sugar was 278 mg.% and the C.S.F. protein was 75 mg.%. He was treated with a low carbohydrate diet, but after three weeks he died suddenly of a pulmonary embolus. I carried out a post-mortem examination. Sections of the spinal cord at the most affected level show only a little chromatolysis of anterior horn cells, without any definite fall-out of cells. The impact of the disease certainly does not appear to fall primarily on the spinal cord.

Garland has always emphasized that not only may the diabetes be symptomless but that gross neurological defect may be present with diabetes that can only be detected by means of a glucose tolerance test, and perhaps only doubtfully then. He (Garland, 1957) mentions one patient with involvement of bulbar muscles and suggests that some patients with "motor neuron disease" may have diabetic amyotrophy and that the former disease may not be a distinct entity. This possibility had been brought to my attention by the following case. A woman of 60 had a six months' history of progressive asymmetrical weakness of the legs accompanied by pain. At this time weakness and wasting were confined to the legs, the tendon reflexes were absent, the plantars flexor and there was no sensory loss. Fasciculation was present but was not marked. The C.S.F. protein was normal. Among other investigations which were not helpful a glucose tolerance test was done and repeated (Fig. 2). It was slightly but definitely abnormal and of the steeple type specifically mentioned by Garland (1957). Treatment with carbohydrate restriction and later insulin was quite ineffective. The wasting progressed, and after a further four months caused her death from spinal respiratory paralysis. The spinal cord presented a very different appearance from that of the previous case, showing virtual destruction of the anterior horn cells typical of motor neuron disease. Although these two conditions may be clinically very similar, pathologically they appear to be distinct.

I have carried out glucose tolerance tests on 11 cases of motor neuron disease. This test is notoriously affected by factors such as preceding diet, infection, drugs, thyroid disease, the method of collection of specimens and of estimation of the blood sugar; in fact nearly every conceivable factor except the size of the patient and of the dose of glucose, which seem to matter little. These tests were done with 50 grams of glucose using the Folin and Wu method on capillary blood. In most cases pains were taken to exclude extraneous factors and the tests were repeated in the more abnormal cases. It can be seen (Fig. 3)

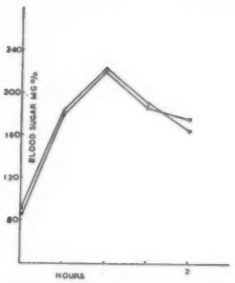



FIG. 2.—Glucose tolerance tests in a case of atypical motor neuron disease.

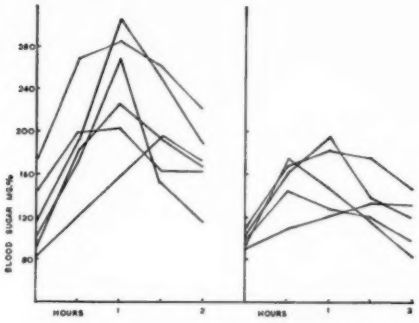



FIG. 3.—Glucose tolerance tests in 11 cases of motor neuron disease.

that although the fasting blood sugar was abnormal in only one case, approximately half the curves are abnormal. I have not found any correlation between the nature of the curve and any clinical feature. It is extremely doubtful whether these curves are of any significance in the causation of the disease and I have not yet carried the investigation any farther. Their immediate significance appears to be that it may not be wise to give a good prognosis in the presence of muscular wasting and an abnormal glucose tolerance curve. Most of the patients figuring on this chart are now dead.

In such investigations we are very much dependent on our biochemical colleagues. I do not think that this dependence makes the work of the clinical neurologist any the less important. It is necessarily the clinician who must pose the questions and to do this he must endeavour to understand, at least in broad outline, what the biochemist has to offer.

## REFERENCES


ALLAN, J. D., CUSWORTH, D. C., DENT, C. E., and WILSON, V. K. (1958) *Lancet*, **i**, 182.
BARON, D. N., DENT, C. E., HARRIS, H., HART, E. W., and JEPSON, J. B. (1956) *Lancet*, **ii**, 421.
BERGREN, W. R., DONNELL, G., and KALCKAR, H. M. (1958) *Lancet*, i, 267.
BICKEL, H., GERRARD, J., and HICKMAN, E. M. (1954) *Acta pædiat., Stockh.*, **43**, 64.
——, SCHULTZE, H. E., GRÜTER, W., and GÖLLNER, I. (1956) *Klin. Wschr.*, **35**, 961.
COATES, S., NORMAN, A. P., and WOOLF, L. I. (1957) *Arch. Dis. Childh.*, **32**, 313.
CONN, J. W., LOUIS, L. H., FAJANS, S. S., STREETER, D. H. P., and JACKSON, R. D. (1957) *Lancet*, i, 802.
DAVIS, B. D. (1954) *Res. Publ. Ass. nerv. ment. Dis.*, **33**, 23.
DEAN, G., and BARNES, H. D. (1958) *Brit. med. J.*, i, 298.
DENT, C. E. (1957*a*) *Amer. J. Med.*, **22**, 671.
—— (1957*b*) *Arch. Dis. Childh.*, **32**, 363.
DINE, M. S. (1956) *Amer. J. Dis. Child.*, **92**, 15.
GARCIN, R., and LAPRESLE, J. (1950) *Sem. Hôp. Paris*, **26**, 3404.
GARLAND, H. (1955) *Brit. med. J.*, ii, 1287.
—— (1957) In: Modern Trends in Neurology. Editor: D. Williams. London; p. 229.
——, and TAVERNER, D. (1953) *Brit. med. J.*, i, 1405.
GREENFIELD, J. G. (1954) *Proc. R. Soc. Med.*, **47**, 150.
HSIA, D. Y.-Y., DRISCOLL, K. W., TROLL, W., and KNOX, W. E. (1956) *Nature, Lond.*, **178**, 1239.
——, KNOX, W. E., and PAINE, R. S. (1957) *Amer. J. Dis. Child.*, **94**, 33.
MARSTON, H. R. (1952) *Physiol. Rev.*, **32**, 66.
MATTHEWS, W. B. (1957) *J. Neurol. Psychiat.*, **20**, 172.
PETERS, H. A., WOODS, S., EICHMAN, P. L., and REESE, H. H. (1957) *Ann. intern. Med.*, **47**, 889.
SCHWARTZ, V., HOLZEL, A., and KOMROWER, G. M. (1958) *Lancet*, i, 24.
SJÖGREN, T., and LARSSON, T. (1957) *Acta psychiat., Kbh.*, **32**, suppl. 113.
WALSHE, J. M. (1956) *Amer. J. Med.*, **21**, 487.
WATSON, C. J., and SCHWARTZ, S. (1941) *Proc. soc. exp. Biol. N.Y.*, **47**, 393.
WOOLF, L. I., GRIFFITHS, R., MONCRIEFF, A., COATES, S., and DILLISTONE, F. (1958) *Arch. Dis. Childh.*, **33**, 31.
WORSTER-DROUGHT, C., WHITE, J. C., and SARGENT, F. (1953) *Brit. med. J.*, ii, 114.


**Dr. R. T. C. Pratt** (London) read a paper on *Genetic Aspects of Metabolic Disorders of the Nervous System.*

*June* 27 and 28, 1958]

MEETING IN OXFORD WITH THE ROUMANIAN NEUROLOGISTS

## PROGRAMME

**Traumatic Carotid Thrombosis.**—Dr. T. D. R. HOCKADAY.

**Copper Metabolism in Normal Adults and in Clinically Normal Relatives of Patients with Wilson's Disease.**—Dr. MARIELLA FISCHER-WILLIAMS.

**Variations and Abnormalities of Cerebral Arteries.**—Dr. A. SOFLETEA.

**Some Considerations of the Physiology of Motor Neurons.**—Dr. JULIA UNGER.

**Intramedullary Spinal Tumour.**—Mr. J. PENNYBACKER.

**A Head Injury Service.**—Mr. WALPOLE LEWIN.

**Constitutional Indifference to Pain.**—Dr. MACDONALD CRITCHLEY.

**The Action of Chlorpromazine on Cortical and Peripheral After-effects Induced by Cortical and Reticular Stimulation.**—Professor KREINDLER.

**Effects of Activity of Cortical Pyramidal Neurons on the Excitability of their Neighbours.**—Dr. CHARLES PHILLIPS.

**The Cervical Spinal Canal in Syringomyelia.**—Dr. J. D. SPILLANE.

**Adrenal Activity in Spinal Paralysis.**—Dr. R. ROBINSON (introduced by Dr. L. GUTTMANN).

**Film of Conditioned Reactions in Decorticate Animals with Intact Rhinencephalon.**—Dr. CINCA.

# Section of Proctology

President—HENRY R. THOMPSON, M.A., M.B., F.R.C.S.

[*May* 14, 1958]

## DISCUSSION ON COMPLICATIONS OF EXCISION OF THE RECTUM

**Dr. Ronald Jarman** (London): *Problems of Anæsthesia*

The complications which might arise during anæsthesia are usually due to the general condition of the patient such as age, arteriosclerosis, bronchial and so on, not the anæsthetic itself, except in rare cases of sequelæ following spinal anæsthesia such as headaches, backaches, trouble with the bladder and minor paralyses.

It is now more than twenty-five years since I established the Etherington Wilson technique of giving Nupercaine spinal anæsthesia (*Proceedings* (1947), **40**, 263, 266). The late W. E. Miles performed his first abdomino-perineal operation under ether from a Clover's inhaler, and it was not until 1919 that Stovaine was used as a spinal anæsthetic with or without nitrous oxide and oxygen. Due to the short-acting time of Stovaine the technique was improved by giving a sacral block using Novocain 2%, anything from 20 to 40 ml., though with larger amounts it was thought advisable to use the 1% solution of Novocain.

In 1929 I used Spinocain with gas and oxygen. In 1930 Nupercaine was used for this operation and three strengths were tried, namely, 1 : 1,000, 1 : 1,500 and 1 : 2,000. In 1932, it was recognized that the 1 : 1,500 dilution of Nupercaine was that of choice, and it has been the spinal anæsthetic that I have used in a large number of cases.

To-day, I use thiopentone and spinal Nupercaine for training, and am likely to go on using this technique, though I must point out that it is essential to allow students and junior anæsthetists to give intravenous anæsthesia together with the various relaxants, the patient being tubed, and control anæsthesia adopted.

A generation has passed since I started this thiopentone-spinal technique, and it is realized that a large number of students and would-be anæsthetists have never seen a spinal anæsthetic given. Yet this type of anæsthesia is still popular in parts of this country and it has a great following in the United States. Unfortunately, there are anæsthetists who have strong views with regard to spinal anæsthetics and who have decried the method so that it takes someone with a reasonable amount of experience to advocate its use.

Over the past ten or twelve years it has been part of the technique to give an intravenous drip of either whole blood or saline and glucose. This method gives a great deal of confidence to the younger surgeon and the less experienced anæsthetist, and it is the method of choice for all major operations whether a spinal anæsthetic has been given or the patient is under the influence of relaxants such as Tubarine or Flaxedil.

On reading through the remarks that I made some eleven years ago as compared to my methods to-day, I find they have hardly changed.

**Dr. W. Kirk Rae** (London): *Problems of Anæsthesia for Synchronous Combined Excision of Rectum*

That there are many problems in anæsthesia for the operation of excision of the rectum is borne out by the striving of anæsthetists with modified techniques to provide better, safer and more controllable anæsthesia, for this rather formidable procedure.

I shall give the results of a review of personal cases anæsthetized at St. Mark's Hospital for the synchronous combined excision of the rectum. For convenience, I have selected 700 cases in chronological order between the years 1946 to 1956. From 1946 to 1950, spinal with general anæsthesia was used in 92 cases, and general anæsthesia, incorporating various relaxant drugs, was used in 127 cases. From 1951 to 1956 there were no spinal anæsthetics used for this operation.

Briefly, the spinal technique consisted of a lumbar puncture in the left lateral horizontal position, followed by Nupercaine 1 : 200 with 6% glucose with an average dose of 1·4 ml. after a thiopentone induction dose (average dose 12 ml. 5% solution). All patients were intubated and maintained in anæsthesia with nitrous oxide.

From 1946 until 1950, of the 127 general anæsthetics given, 56 had cyclopropane ether sequence; 22 had cyclopropane with gallamine triethiodide (average dose 146 mg.); 19 had cyclopropane with decamethonium iodide (average dose 8 mg.); and 30 had nitrous oxide with *d*-tubocurarine (average dose 18 mg.). All these cases had a thiopentone induction and were intubated with cuffed Magill tubes.

From 1950 until 1956, of the 481 general anæsthetics given, 279 had nitrous oxide with curare (average dose 40 mg.); 150 had gallamine triethiodide (average dose 160 mg.); and 52 had curare (average dose 25 mg.) with hexamethonium bromide hypotensive technique.

My chief disappointment with the spinal anæsthetic is its effect on the cardiovascular system. Even although the actual blood-pressure readings can be corrected by various vasopressor agents, I feel that the patient is at risk with the spurious blood pressure readings which are so frequently followed by secondary circulatory collapse. Also I know of no way of foretelling how much the spinal anæsthetic will affect the blood pressures in a given patient. With a general anæsthetic there is much more control over the blood pressures; and the cardiovascular function, unless disturbed by the operation (especially with blood loss), remains closely within normal limits.

The average fall in the systolic blood pressures in the 92 spinal cases was 40% of normal, and the average fall in the diastolic blood pressures was 26%.

Now in contrast are those of patients with their operation under general anæsthesia only: Systolic average fall, 7·4%. Diastolic, 3·8%.

I feel that disturbance by the surgical procedure of the cardiovascular system in relation to the production of shock and neurocirculatory asthenia creates a sufficient problem without the addition of an initial upset in the cardiovascular system by the spinal anæsthetic even before the operation begins. I believe that it is safer for the patient if the blood pressures are kept as near normal as possible during the operation, without vasopressor agents, and to this end an adequate and properly timed blood transfusion should be carried out in every case. By properly timed, I mean that the blood volume should be kept constant, with transfusion adjusted to the rate and quantity of the blood loss, and the perineal wound should not be closed if the blood pressures are markedly below normal, as this could clearly encourage the incidence of reactionary hæmorrhage. It was found that from 1946 until 1950 the average amount of blood given during the operation was 1¼ bottles (the other ¾ bottle average being given subsequently in the ward)—a total of 2 bottles. From 1950 until 1956, the average amount of blood given per case during the operation was 2¼ bottles (the other ¾ bottle average being given in the ward after)—a total of 3 bottles. This increase in the amount of blood given for the synchronous combined excision of the rectum is, of course, partly related to the abandonment of the spinal anæsthetic, which by inducing low blood pressures minimized blood loss, but also to our improved knowledge of blood volume requirements; we now realize that in the past patients generally lost more blood than was thought and replacement was tardy. At this stage, I would like to say how impressed I was with the work of Ruscoe Clarke and his colleagues at the Birmingham Accident Hospital on shock and blood loss.

It is essential for this operation that some safe form of mechanical assistance should be available to enable the anæsthetist to transfuse blood as rapidly as it can be lost from the wounds. At St. Mark's Hospital we have used the Martin transfusion pump. On more than one occasion I am confident that this device has saved the lives of the patients, as precipitant falls in blood pressure have been rapidly corrected by pumping in blood at the rate of 1 bottle (500 c.c.) in 3 or 4 minutes.

*The Mortality Figures*

These patients were selected because of the closeness in time to the operation and anæsthetic when they died. Patients who died after an interval of "apparent recovery" from the operation and anæsthetic have not been included in this study.

MORTALITY FIGURES—1946 to 1956

*Number of Cases* 700. *Number of Deaths* 8. *Approximately* 1%

| | | Analysis |
|---|---|---|
| 1947. | 1 death | within 1 hour of the operation |
| 1948. | 1 „ | „ 17 hours „ „ „ |
| 1949. | 3 deaths, | 1 within 17½ hours of the operation |
| | | 1 „ 2 „ „ „ „ |
| | | 1 „ 48 „ „ „ „ |
| 1950. | 2 „ | 1 „ 2½ „ „ „ „ |
| | | 1 „ 16 „ „ „ „ |
| 1951. | 1 death | „ 3 „ „ „ „ |
| 1952 to 1956. | No deaths in 481 cases | |

There were 4 deaths during 1946 to 1951 in 92 cases of spinal anæsthesia and 4 deaths during this period in 127 cases of general anæsthesia (including 1 death during the use of hypotensive anæsthesia, which has a similar effect on the cardiovascular system to the spinal). Therefore, it would seem that in the straight general anæsthetics given there were 3 deaths in 127 cases compared with 4 deaths in 92 cases of spinals.

I hope I have shown that in this series of 700 personal cases it would appear that the spinal anæsthetic carries a higher overall risk than the general anæsthetic with the use of relaxant.

It is my opinion that, in a patient who is medically fit, the use of the spinal anæsthetic

or a general anæsthetic from the point of view of immediate risk matters little, but in a patient who has a history of impairment of the cardiovascular system and/or the respiratory system, I feel, from this short study, that the general anæsthetic with relaxants is more controllable and would be safer in the synchronous combined excision for such a patient. In this connexion, in more recent years there has been a tendency amongst surgeons to perform high ligation of the inferior mesenteric artery. This is sometimes accompanied by some anxiety regarding the viability of the colon. In these cases again, a general anæsthetic, in my opinion, is better because the blood pressures are maintained, and this makes it easier for the surgeon to decide whether the colon, after such high ligation, is viable. Also, in recent years there has been a tendency to perform a restorative type of resection, having opened the abdomen, where the pre-operative diagnosis suggested a synchronous or abdomino-perineal excision. The restorative resection takes almost twice as long in time as the abdomino-perineal, and in this connexion again the general anæsthetic is preferable, because the spinal anæsthetic would not be satisfactory for such a long time.

My thanks are due to my colleagues at St. Mark's Hospital for all their help.

**Mr. Gordon S. Ramsay** (London): *The Perineal Wound*

This paper is based on a study of cases operated upon at two hospitals—the Gordon and the Royal Marsden—during the period 1946 to 1957. There were 657 cases (Table I), the majority being abdomino-perineal excisions.

TABLE I.—COMPLICATIONS OF EXCISION OF THE RECTUM: THE PERINEAL WOUND. COMBINED GORDON AND ROYAL MARSDEN SERIES 1946–57

| | | |
|---|---|---|
| Abdomino-perineal excision | 581 | Total 657 |
| Abdominal excision (extended Hartmann) | 56 | |
| Perineal excision | 20 | |

I have included 56 abdominal excisions (extended Hartmann operation) because, although they did not have a perineal wound except when one was made to provide drainage, the problems of the pre-sacral space, with which I am mainly concerned, were much the same in these as in the other cases. There were, as one would expect nowadays, few perineal excisions.

The operative mortality was 10·3% (Table II). 59 patients died from causes such as pulmonary embolus, coronary thrombosis, pneumonia, shock and peritonitis, and 9 (1·3%) died as the direct result of a complication of the perineal wound.

TABLE II.—COMPLICATIONS OF EXCISION OF THE RECTUM: THE PERINEAL WOUND. COMBINED GORDON AND ROYAL MARSDEN SERIES 1946–57 (657 CASES)

*Operative Mortality*

| | |
|---|---|
| From perineal wound | 9 (1·3%) |
| From other cause | 59 (9%) |
| Total | 68 (10·3%) |

TABLE III.—THE PERINEAL WOUND

*Complications*

| | Non-fatal | Fatal |
|---|---|---|
| Infection | | |
| Slight | 22 | 0 |
| Abscess | 15 | 0 |
| Severe | 3 | 4 |
| Hæmorrhage | | |
| Reactionary | 2 | 2 |
| Secondary | 4 | 2 |
| Delayed healing | | |
| Breakdown | 27 | 0 |
| Persistent sinus | 13 | 0 |
| Pain | 16 | 0 |
| Other | 5 | 1 |
| | 107 (16%) | 9 (1·3%) |

The cases with complications have been grouped according to their main complication (Table III). Few patients had more than one complication and I feel that this method presents the clearest picture of the state of affairs. Non-fatal complications of the perineal wound occurred in 16% of cases as compared with 12% (21 out of 176 cases) of a series reported by Buckwalter *et al.* (1955). Other complications occurred in 4% of patients and among these were 10 cases of perineal urinary fistula which have been excluded because this is primarily a urinary complication. I would stress that the complications of the perineal wound accounted for the greater part of the post-operative morbidity in this series.

Cases with infection fell into three groups, i.e. those with slight infection, little or no constitutional upset but whose wounds discharged some pus. The commonest organisms found were *B. coli* and *Staph. aureus*, usually in combination, sometimes separately, but proteus, *B. welchii*, diphtheroids, *Strep. faecalis* and *Staph. albus* were all found on occasions. They all responded to simple measures and the delay in healing was minimal.

I have put abscesses under a separate subheading because they all occurred late—a few months to three years after operation—and they were associated especially with abdominal excision—8 of the 15 cases were those who had had an extended Hartmann operation.

There was a high mortality among those who developed severe infection, the essential feature of which was spread beyond the immediate vicinity of the wound to involve the retro-peritoneal tissues widely. The organisms were chiefly anærobic and there was one fatal case of gas gangrene who died four days after an A.P. excision.

Ten patients bled seriously and of these 4 died. One fatal case bled from a vein on the side wall of the pelvis and another from "a branch of the internal iliac artery". In the other 2 who died, severe reactionary hæmorrhage was controlled in one, but the patient succumbed, and the other died following a secondary hæmorrhage. The remainder all recovered after the bleeding had been controlled either by packing or by tying a bleeding point.

Delayed healing is one of the major problems, and although some infection was present in many of these cases, gross infection was not a feature. Those whose wounds broke down were usually elderly, their average age was 67 compared with an average age of 61 for all patients with complications. Obesity and diabetes were sometimes contributory factors. 8 were re-sutured and healed well, 3 developed a recurrence in the wound, and 16 healed eventually with conservative treatment.

There were 13 cases of persistent sinus and in 7 a definite cause was found. A retained foreign body was the cause in 3 cases: in one, a piece of catgut, in another a piece of gauze and in the third some cotton-wool. In each case the offending substance was removed several months after the original operation. There was one mucous fistula after a perineal excision and in the other 3 cases the cause was a recurrence of the disease. Of the 6 cases in whom a definite cause could not be found, 3 were operated upon and a piece of the track was examined histologically but all showed chronic inflammation only. The sinus sometimes persisted for more than a year.

It is often said that persistent pain after excision of the rectum is found eventually to be due to a recurrence. It was true of 7 of these patients and in 4 of them there were metastases in bone. It is important to remember that the pain may precede radiological evidence of bone involvement by several months and repeated examinations may be necessary before the diagnosis is confirmed. The cause is not always so sinister but may be difficult to diagnose. One man of 68 who had an A.P. in August 1955 developed pain in June 1956. No cause could be found but the pain persisted and in January 1957 his perineal scar was excised, no recurrence was found and the pain continued. His symptoms were eventually relieved, to a great extent, when some osteoarthritis of his spine was treated with physiotherapy. Another patient who developed severe perineal pain two years after excision of the rectum was found to have a prolapsed intervertebral disc. In 7 cases the cause for the pain was never found and they were treated symptomatically with varying degrees of success. This interesting group of patients would, I think, repay further study.

Finally the miscellaneous group. There were 3 cases of prolapse of the small bowel through the pelvic floor and they occurred eight, twenty-four, and twenty-eight days after operation and not as one might have expected, in the early post-operative period. The fatal case was a man of 70 whose pelvic floor gave way eight days after an A.P. He developed a small bowel fistula into the perineal wound and did not survive. The next patient strangulated 6 in. of small gut through a small hole; it is possible, of course, that the prolapse had taken place at a much earlier date. The last patient had widespread disease and a urinary fistula, factors which probably produced non-healing of the pelvic floor.

There was 1 case of peritonitis which was caused by some of the fluid at the first perineal irrigation being forced through the pelvic floor into the peritoneal cavity. She responded to conservative treatment and the irrigations were resumed one week later.

There were 2 cases of perineal hernia. The first patient was a man aged 73 who developed quite a large hernia after A.P. excision. For reasons which are not stated in the notes, surgical repair was not attempted and his symptoms were relieved by a support.

The condition occurs more commonly in obese women as in the second patient, aged 64, whose hernia also occurred after A.P. excision. A repair *per abdomen* was done using the uterus to reinforce the closure of the sac but the hernia recurred. A synchronous combined abdomino-perineal operation was then performed and the hernia repaired with strips of fascia from both thighs after the method described by Gabriel (1948). Once more recurrence took place and she too was then given a support which relieved her symptoms partially.

Some degree of bulging of the perineum and often quite a marked impulse on coughing is common after excision of the rectum but a hernia large enough to cause symptoms is very rare. Cattell and Cunningham (1944) reported the first case at the Lahey clinic in 800 resections of the rectum. They cite the removal of the coccyx as the principal predisposing factor in the development of the hernia. The fate of the coccyx was only

rarely recorded in the notes and I cannot therefore give accurate figures, but I know that in the majority of cases it was removed. In view of the low incidence of hernia, it is difficult to believe that this factor is of paramount importance. When one remembers that quite a large hernia can occur through an intact levator ani muscle it is strange that it does not happen more often after the whole of the pelvic diaphragm has been removed.

The successful healing of the perineal wound depends upon the speed and completeness of obliteration of the pre-sacral space (Fig. 1). Its closure is effected mainly by the structures forming the anterior wall dropping back to make contact with the concave surface of the sacrum. The mobility of the various structures, however, is practically never sufficient to make this contact complete. The prostate and vesicles, for example, have a range of movement of about 5 cm. in a vertical plane but cannot usually be made to touch the front of the sacrum either at operation or in the cadaver. (The same applies to the uterus and posterior vaginal wall in the female.)



FIG. 1.—To show pre-sacral space after removal of rectum.

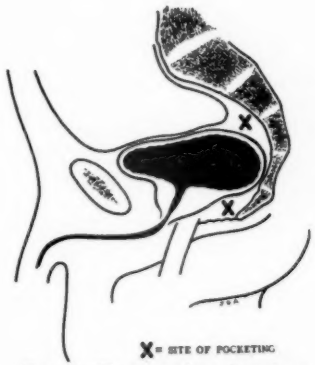



FIG. 2.—To show sites of pockets above and below the bladder.

The wound heals partly by granulation and must therefore be drained, and if open drainage is used, it will always be infected to a slight extent.

Sometimes the posterior bladder wall alone meets the sacrum and thereby gives rise to the formation of pockets in the upper and lower part of the wound (Fig. 2). I believe this to be a frequent cause of abscess formation in these sites. These pockets can sometimes be seen in lateral radiographs of the sacrum.

Now there is still no universal agreement as to the best method of dealing with the perineal wound, but there has been a tendency in recent years to discard the traditional pack in favour of suture around a drain.

Rankin and Graham (1950) advocate packing with oil-silk and gauze, but Crile and Robnett (1950) advocate suture around a catheter, thrice daily aspirations and instillation of penicillin solution. They say that their patients are discharged on the twelfth day and claim complete closure in 23 of 25 cases. Hughes (1957) is in favour of tube drainage and under-water seal. Other authors, including Beahrs and Congdon (1957) use a catheter and continuous suction. Beahrs and Congdon compared a series of cases treated by this method with a larger series treated with a pack and found that those treated by the method described healed more quickly, had a shorter convalescence and a lower incidence of persistent sinus than the cases treated with the pack.

A pack is used to support the newly made pelvic floor and to control oozing, but in most cases neither function is necessary. The walls of the cavity become rigid with œdema after quite a short time and their apposition after the removal of the pack is thus impeded. Everything should be done to encourage the formation of healthy granulation tissue, and the use of diathermy and of antiseptics which produce coagulation of the superficial layers must hinder this process and should therefore be avoided. Careful hæmostasis is essential and time spent achieving this should not be grudged. Catgut, and not unabsorbable ligatures, should be used and bleeding from the peri-prostatic venous plexus can be most satisfactorily controlled by a running atraumatic suture. I prefer to use a corrugated rubber drain, extending well up behind the bladder and emerging from the most dependent part of the wound, i.e. anteriorly. The drain is removed on the third post-operative day and thereafter the wound is irrigated twice daily with saline followed by the instillation of 30 ml. of

Furadantin solution. Finally I would stress the importance of careful examination of the wound with a probe every few days to guard against the formation of pockets.

Attention to these points may help in some measure towards the reduction of infection and delayed healing—the two commonest complications of the perineal wound.

## REFERENCES


BEAHRS, O. H., and CONGDON, G. H. (1957) *Surg. Clin. N. Amer.*, **37**, 999.
BUCKWALTER, J. A., SHROPSHIRE, R., and JOINER, B. A. (1955) *Surg. Gynec. Obstet.*, **101**, 483.
CATTELL, R. B., and CUNNINGHAM, R. M. (1944) *Surg. Clin. N. Amer.*, **24**, 679.
CRILE, G., JR., and ROBNETT, A. H. (1950) *Cleveland Clin. Quart.*, **17**, 5.
GABRIEL, W. B. (1948) The Principles and Practice of Rectal Surgery. 4th edit. London; p. 386.
HUGHES, E. S. R. (1957) Surgery of the Anus, Anal Canal and Rectum. Edinburgh; p. 245.
RANKIN, F. W., and GRAHAM, A. S. (1950) Cancer of the Colon and Rectum. 2nd edit. Springfield; p. 298.


**Mr. J. M. Davis** (London): *Complications of the Colostomy* (Abridged)

1,235 excisions of the rectum for carcinoma, with the formation of a terminal colostomy, have been performed at St. Mark's Hospital in the ten-year period 1948–1957. 137 (11·1%) patients developed colostomy complications. 20 patients had multiple complications and 5 patients died as a result of colostomy complications.

The main purpose of this paper is to study the influence of three recent developments of technique on the incidence of certain complications. These three developments are: (1) Direct suture of the colostomy to the skin of the abdominal wall as advocated by Patey (1951); (2) high ligation of the inferior mesenteric artery; (3) the trephine method of formation of the colostomy hiatus.

The method of formation of the colostomy varied with different surgeons and with the passage of time. The colostomy site, in the majority of cases, was about 1 in. above a left-sided McBurney point through a separate stab or trephine incision. 14 colostomies were sited in the mid-line or through the main incision and 81 at the level of the umbilicus through the rectus sheath. In the two latter groups the lateral space was not closed. In all other cases it was closed. Direct suture was performed in 290 cases and high ligation of the inferior mesenteric artery in 129 cases.

The complications fall into two main groups—early and late (Table I).

TABLE I.—COLOSTOMY COMPLICATIONS

| *Early* | | *Late* | |
|---|---|---|---|
| Retraction: Complete (intraperitoneal) | 6 | Stenosis | 82 |
| Partial (subcutaneous) | 11 | Hernia requiring operation | 12 |
| Sloughing (includes 8 listed under retraction) | 12 | Prolapse | 3 |
| Primary colostomy wound infection | 11 | Submucous abscess | 1 |
| Obstruction (tight hiatus 2; lateral space 2; adhesions 1) | 5 | | 98 |
| Peritonitis in region of colostomy | 3 | | |
| Visceral prolapse through colostomy hiatus | 5 | | |
| Colostomy fistula | 2 | | |
| Secondary hæmorrhage | 4 | | |
| | 59 | | |

*Effect of Direct Suture on the Incidence of Complications*

When Mr. Patey advocated direct suture with mucocutaneous apposition, he suggested that the fears of colostomy retraction, colostomy sloughing and colostomy wound infection had been exaggerated. He felt that direct suture would decrease the incidence of stenosis and, also, that by eliminating the œdematous and sometimes sloughing mass of projecting colon, the incidence of post-operative distension, colostomy dysfunction and possibly paralytic ileus would decrease.

TABLE II

| | | Without direct suture | With direct suture | % Difference |
|---|---|---|---|---|
| All cases | 1,235 | 945 | 290 | |
| Developed stenosis | 82 | 73 (7·7%) | 9 (3·1%) | −4·6% (S) |
| Developed retraction | 17 | 13 (1·4%) | 4 (1·4%) | nil |
| Developed primary infection | 11 | 6 (0·6%) | 5 (1·7%) | +1·1% (NS) |
| Developed paralytic ileus | *16 | 14 (5·1%) | 2 (0·7%) | −4·4% (S) |

(S) = Statistically significant. (NS) = Not statistically significant.
*From last five years only—564 cases: 274 without direct suture.

The significant fall in the incidence of stenosis from 7·7% to 3·1% (Table II) is almost certainly the result of the method of direct suture. This is due to the elimination of the

fibrous tissue contracture that develops in the granulation tissue forming round the projecting colon.

The incidence of retraction is unchanged. Of the 4 cases where retraction occurred after direct suture, 2 were complete with intraperitoneal soiling in the first three post-operative days. These 2 cases would probably have been prevented by some other method of fixation. The 2 remaining cases were partial and occurred later and would probably have happened whatever method had been used.

There has been some selection in the cases considered suitable for direct suture. If every case had been done by this method the incidence of retraction would undoubtedly have been much higher. The contra-indications to direct suture that have been accepted are: obstruction; excessive fæcal loading (as the bowel contracts to expel these fæces it also shortens and tension increases); doubt about the blood supply; gross obesity and any other condition giving a shortage of colon. The absolute essentials for direct suture are a good blood supply and the absence of tension.

The small increase of primary colostomy wound infection from 0·6% to 1·7% (Table II) is not statistically significant. Of the 5 cases of infection after direct suture, 2 had paracolostomy abscesses requiring incision and one had an intracuticular infection causing spreading skin gangrene which had to be excised. These 3 cases were almost certainly due to the method of direct suture. The 2 remaining cases may not have been due to the method but are included in the figures. They were staphylococcal infections and were associated with main and perineal wound infections in the same patients.

Although the fall in the incidence of paralytic ileus from 5·1% to 0·7% (Table II) is statistically significant, care must be taken with the interpretation of this difference. Paralytic ileus has many unknown ætiological variables. In addition, the group not done by direct suture contains a number of cases deliberately rejected from the "direct suture group" because of conditions which may well have predisposed to paralytic ileus, i.e. heavy fæcal loading, tension on the colon, or doubt about the blood supply. Nevertheless, this difference does parallel the clinical impression that direct suture has reduced the cases of post-operative abdominal distension and colostomy dysfunction. The use of a trephine hiatus has also probably contributed to this improvement.

The advantages, then, of direct suture are a significant fall in the incidence of stenosis and a probable fall in the incidence of paralytic ileus and colostomy dysfunction. The dangers of retraction are not increased provided the method is not used when contra-indicated. A statistically unmeasurable advantage is the elimination of the œdematous and sometimes offensive colostomy mass and its effect on the patient's comfort and morale in the post-operative period. The disadvantage is a small increase in the incidence of infection. There are two other cases which must be weighed in the disadvantage scale. One was a case of colostomy prolapse in the post-operative period due to a technical fault whereby excessive eversion of the colon had occurred whilst direct suture was being performed. In another case, prolapse of a loop of ileum alongside the colostomy was masked by direct suture and was not diagnosed until it caused obstruction on the seventeenth post-operative day.

But, regardless of the figures, the rapid acceptance and continuing popularity of the method speak for themselves. The percentage of cases performed each year by direct suture, by the five surgeons who have been giving it a trial, has risen from 41% in 1953 to 95% in 1957.

*Effect of High Ligation of the Inferior Mesenteric Artery on the Incidence of Complications*

TABLE III

| | | Without high ligation | With high ligation | % Difference |
|---|---|---|---|---|
| All cases .. .. | 1,235 | 1,106 | 129 | |
| Developed retraction .. | 17 | 13 (1·2%) | 4 (3·1%) | +1·9% (NS) |

(NS) = Not statistically significant.

The rise in the incidence of retraction in this group from 1·2% to 3·1% (Table III) is not statistically significant. 2 of the 4 cases, after high ligation, were intraperitoneal. In 1, complete sloughing occurred; in the other, the colon was viable but there was insufficient length left to construct the colostomy without tension. The 2 remaining cases of retraction were partial, requiring operation in the third and fourth week respectively. In 1 of these cases the terminal 5 cm. of the partially retracted colon was very stenosed and there was gross muscle thickening similar to that seen in Volkmann's ischæmic contracture.

The influence of high ligation on stenosis is best seen by considering only those cases performed by direct suture. This eliminates the large number of cases of stenosis caused by fibrous contraction following methods without direct suture.

TABLE IV

| | | Without high ligation | With high ligation | % Difference |
|---|---|---|---|---|
| Cases performed by direct suture .. | 290 | 203 | 87 | |
| Developed stenosis .. | 9 | 4 (2·0%) | 5 (5·7%) | +3·7% (NS) |

(NS) = Not statistically significant.

The increase of the incidence of stenosis from 2% to 5·7% (Table IV) is not statistically significant because of the small size of this group but it probably truly reflects the small number of cases that develop stenosis due to ischæmic changes, some of which may be unrecognized in the post-operative period.

The disadvantages, then, of high ligation are a small increase in the incidence of retraction and in the incidence of stenosis. When enough cases have been accumulated for a sufficiently long time to assess its advantages, they must obviously be weighed against these two disadvantages.

*The "Ideal" Colostomy*

A method of colostomy formation, now most frequently used at St. Mark's, was described, stressing the value of a trephine hiatus, the avoidance of tension and the preservation of the blood supply, the importance of closure of the lateral space and the ease of this manœuvre if performed from the right-hand side of the patient prior to withdrawal of the colon through the colostomy hiatus, the advantages of direct suture when indicated and the use of a glass rod through the mesocolon when direct suture is contra-indicated, and the importance of regular post-operative assessment of viability.

I should like to thank all the surgical staff at St. Mark's Hospital whose ideas, opinions and techniques I have borrowed and quoted freely, and particularly Mr. H. R. Thompson for his advice on the preparation of this paper.

REFERENCE.—PATEY, D. H. (1951) *Proc. R. Soc. Med.*, **44**, 423.

**Mr. D. Innes Williams** (London): *Genito-urinary Complications*

This contribution is concerned with the late effects upon the urinary tract, as they are seen by the urologist, and the immediate post-operative management is not discussed. The most important complication is therefore retention of urine, a disorder which so readily brings to mind the enlarged prostate that there is a danger that it will be discussed entirely in terms of when to perform prostatectomy. Many special factors are concerned in retention after excision of the rectum however, factors which make retention after this more likely than after any other lower abdominal or perineal operation. Local trauma—bruising of the bladder base, prostate and urethra—undoubtedly plays an important part, as it does after colporrhaphy in the female. The amount of trauma inflicted will depend upon the skill of the surgeon, the size of the growth and the extent of the dissection. Obviously therefore the more radical the operation, and the higher the operability rate, the greater will be the incidence of post-operative retention and although gentleness is extremely desirable as a surgical habit, it is not the most important consideration in cancer surgery.

*The displacement of the bladder* into the hollow of the sacrum is the next factor to be considered. Excision of the rectum leaves a horrid vacuum which the bladder unfortunately attempts to fill and, in doing so, upsets its own mechanics. The membranous urethra remains a fixed point but the prostate, bladder neck and bladder base fall backwards, straightening out the urethra and flattening the angle between the base of the bladder and the posterior urethra. This alteration of anatomy is of great importance in performing cystoscopy and in later operations upon the prostate: but we are not altogether clear what part it plays in the retention. In the abdomino-anal operation and in pull-through operations, for instance Swenson's procedure for rectosigmoidectomy in Hirschsprung's disease, the fall back of the bladder cannot occur and the incidence of retention is certainly much less but perhaps the trauma to the bladder base is also less. The straightening of the urethra interferes with the sphincteric mechanism and should, if anything, favour incontinence but it should be noted that the bladder is not only displaced, it has lost its supports. A man who attempts to assist micturition by abdominal straining, as is customary in cases of difficulty, will push the bladder downwards instead of simply compressing it within the intact pelvis. The vacuum left by excision of the rectum is a considerable handicap therefore; it may be minimized by packing but it is difficult to see how it can be altogether avoided.

*The problem of the enlarged prostate.*—There are, of course, patients with carcinoma of the rectum who are already on the verge of retention due to prostatic enlargement and in

these rectal excision will certainly precipitate the event. It is tempting in such cases to perform a prostatectomy at the same time as the rectal operation, using the posterior approach as suggested by Pyrah (1951). But there are not now many surgeons in England with experience of perineal prostatectomy, and except in the very fit it seems hazardous to risk the simultaneous appearance of complications of both rectal and prostatic operations. A preliminary prostatectomy also has its attractions, particularly if a preliminary colostomy is performed. The prostatic operation can then be carried out before the urine becomes infected and healing should be rapid. Nevertheless it usually seems more dangerous to postpone the excision of the growth and particularly when the prostatic obstruction is already complicated by stone or urinary infection, a suprapubic cystostomy at the time of the rectal operation and a prostatectomy a month or two later is the safer procedure.

*Cystoscopy in Post-proctectomy Cases*

Next we come to the man who had no pre-operative urinary symptoms and whose prostate was not obviously enlarged when first examined. After operation he may be unable to micturate, he may have the sensation of bladder distension yet even when his general condition is good, when he is out of bed and his wound healed, no urine is passed. In such a case it is easy to believe that prostatic hypertrophy or a minor degree of bladder-neck obstruction is the cause. In the absence of the rectum, the assessment of the prostate must obviously be cystoscopic and this brings us to the question of cystoscopy in post-proctectomy cases. The instrument enters the bladder in an almost straight line, there is no need to depress the eyepiece in order to turn the corner between the bulb and the posterior urethra. Moreover if the eyepiece is depressed into the ordinary position once the instrument is in the bladder, the beak will prize open the posterior urethra and allow a clear view of the trigone continuing down into the urethra as far as the verumontanum. This is a purely mechanical effect and does not indicate "funnelling" or pathological relaxation of the bladder neck. Prostatic enlargement may be recognized from the following features: the angle between the posterior urethra and the trigone is preserved, it is necessary to depress the eyepiece to get the instrument in, and the trigone drops away sharply from the bladder neck. The distance between the bladder neck and the verumontanum is increased above the normal half-inch or so. Anteriorly a cleft between the lateral lobes indicates prostatic enlargement, a posterior cleft can be produced by the simple fall back.

When a prostatic enlargement is found there need be no hesitation in proceeding to its removal by enucleation or transurethral resection. The fall back might seem to make retropubic prostatectomy easier than normal but I have found that the lack of posterior support confuses the normal landmarks and where open operation has been performed, I have used the Harris technique. After either the open or the endoscopic method there is a greater incidence of urinary incontinence than after the ordinary prostatic operations. It might be supposed that the external sphincter, being intact, should maintain continence but the external sphincter is a voluntary muscle and does not exhibit a constant tone. Caine and Edwards (1958) have recently shown that continence after a prostatic operation is dependent upon the elastic recoil of the posterior urethra above the external sphincter which pushes back the urine into the bladder after the detrusor has ceased to contract and it looks as if the removal of the levator ani is the factor which prevents the urethra recoiling in the normal fashion.

Many of these men with retention after proctectomy prove on cystoscopy to have an almost normal prostate, yet where their retention has lasted a long time a minute transurethral resection does sometimes get them going. One wonders whether these are minor examples of nerve trauma but they have a very different prognosis from the fully-fledged case which is easy to recognize, for the bladder passes through distinct phases as it does in the spinal cord injury. In the first phase of the pelvic nerve syndrome there is retention with overflow, in the second the bladder is partially expressible but a large residuum remains, and in the third it is completely expressible and may be continent.

The phase of retention is at first concealed by the routine post-operative drainage but when the catheter is taken out overflow will occur without any sensation of bladder fullness. This absence of sensation, if it occurs in a fit man without any history of bladder trouble, is rather important evidence of nerve trauma. The habit of expressing the bladder, emptying it by external compression only, using the diaphragm and abdominal muscles and without active bladder contraction, is acquired after a few weeks. Although expression is incomplete at first it gradually becomes more effective; while a residual urine remains after expression, incontinence will continue but as time goes on most of these men remain dry by day. Once again, the external sphincter and its associated muscles are intact and functioning, indeed the bulbocavernosus is often used to give an additional push to the urinary stream but these voluntary muscles are not sufficient to maintain continence alone. The diagnosis of nerve damage will be made from the absence of sensation, the expressibility

of the bladder and the relaxation of the bladder neck seen at cystoscopy. Treatment should be conservative, the bladder will become expressible in time; it must be drained by catheter until then and the patient must be instructed in the methods of expression. In a few cases, transurethral resection will hasten the attainment of complete expressibility but the procedure is not often required and may ultimately hinder the attainment of continence. Some men will always require a penile urinal to keep them dry.

The special concern of the rectal surgeon will be the avoidance of nerve injury. It is usually supposed to happen posteriorly where the trunks are few in number and may be damaged if the dissection is carried up behind Waldeyer's fascia. It seems almost incredible, however, that surgeons of experience should make this error and looking over the records of cases in which I have diagnosed nerve injury, it does appear that when any difficulty in dissection occurred, it was anteriorly. Goligher's survey (1951) of the incidence of impotence after excision of the rectum also suggested that partial nerve damage was more common than the ordinary methods of urological diagnosis would suggest, and if the damage is partial, it must almost certainly be anterior or antero-lateral to the rectum, where the nerve fibres are distributed in a diffuse plexus.

Retention then is the most common urinary complication and patience is the most important feature of diagnosis and treatment. The majority of men will recover without further surgery and there should be the greatest reluctance to operate upon the neck of the bladder or prostate, unless prostatic obstruction was already evident before the excision of the rectum. In women prolonged retention is rare and usually inexplicable. I have not encountered a woman with definite evidence of nerve damage but there were two who suddenly recovered normal micturition after the removal of an extraordinarily small amount of tissue from the bladder neck by transurethral resection.

*Urinary infection* is an unfortunate complication of retention in post-proctectomy cases and one which is well worth checking because of its later consequences. I have had 3 cases of vesical calculi appearing some years after rectal excision in chronically infected bladders. Infections almost always accompany prolonged catheterization and we are apt to become resigned to the fact but a number of papers recently have shown how cross-infection can be minimized. The use of polyvinyl tubing in the form of the Gibbon catheter connected to a closed drainage bottle might well be better than the conventional methods (Gibbon, 1958).

*Urinary Fistula*

The late appearance of a urinary fistula in the perineum is another problem upon which the urologist is apt to be consulted: this may be due to a urethral, a vesical or a ureteric fistula. The urethral fistula is a consequence of unsuspected injury of the bulbar region and the leak only occurs after the catheter has been withdrawn, and only on micturition. It has always healed after a further week or ten days of urethral catheter drainage. The vesical fistula is seldom unexpected, it occurs when the bladder was opened at the time of operation and has been inadequately closed. In the absence of prostatic obstruction it too will heal in the end if the bladder is drained but there is some danger that it will leave a permanent rigid diverticulum in the base of the bladder which is apt to maintain a chronic urinary infection. Bladder closure at the time of operation is therefore worth careful attention and at least two rows of continuous suture. The leak from a ureteric fistula is uninfluenced by the presence of a catheter but since it is often due to a stitch or a ligature accidentally placed around a ureter, it may not occur for a week or ten days after the operation. The complication is only likely to arise in a case with a difficult dissection and secondary repair is therefore seldom practicable: the side of the lesion must be identified and usually a nephrectomy performed. Such a patient should be cystoscoped immediately and ureteric catheters passed. Usually a complete obstruction is encountered at the site of the injury but if both catheters go up easily they may be left in position for two or three days to see whether spontaneous healing will occur.

REFERENCES

CAINE, M., and EDWARDS, D. (1958) *Brit. J. Urol.*, **30**, 34.
GIBBON, N. (1958) *Brit. J. Urol.*, **30**, 1.
GOLIGHER, J. C. (1951) *Proc. R. Soc. Med.*, **44**, 824.
PYRAH, L. N. (1951) *Proc. R. Soc. Med.*, **44**, 828.

**Mr. C. I. Cooling** (London): *Genito-urinary Complications of Excision of the Rectum*

My part in this discussion is to present the general clinical experience of genito-urinary complications of excision of the rectum. 369 cases of excision of the rectum have been assessed from those seen at the Gordon Hospital, 1947–57, and include 279 combined abdomino-perineal excisions, 78% by the Miles method and 22% by the synchronous combined approach (Table I).

TABLE I.—EXCISION OF THE RECTUM

| Type | Male | Female | Total |
|---|---|---|---|
| Abdomino-perineal | 157 | 122 | 279 |
| Hartmann .. .. | 10 | 16 | 26 |
| Anterior resection.. | 17 | 25 | 42 |
| Perineal .. .. | 7 | 6 | 13 |
| Sphincter-conserving | 6 | 3 | 9 |
| | 197 | 172 | 369 |

TABLE II.—NORMAL MICTURITION AFTER COMBINED EXCISION OF RECTUM

| | Male | Female |
|---|---|---|
| < 7 days .. | 63% | 81% |
| < 14 days .. | 10% | 9% |
| < 21 days .. | 5% | 5% |
| < 28 days .. | 4% | 2% |
| > 28 days .. | 1% | — |

TABLE III.—INJURIES

Vesico-perineal urinary fistula
A.P.: 3 females
2 males
Perineal: 1 female
1 male
Urethral fistula
A.P.: 2 males
Right ureter ligated
Deliberate: 2 males
Accident: 1 male
1 female

TABLE IV.—PROSTATECTOMY

14 Cases = 7% of males

| | Number | Incontinence |
|---|---|---|
| Perurethral resection after operation .. | 9 | 1 |
| Retropubic excision after operation .. | 2 | 1 |
| Resection with rectum .. .. | 3 | 3 |

The genital complications in the female consisted of 2 cases of pregnancy, both of which were terminated, and a case of perineal excision of the rectum for advanced cancer in the presence of a six-months pregnancy. A live child was born two months later.

In the male, epididymo-orchitis was seen only once and followed a prolonged period of an indwelling catheter for urinary fistula, so that the risk of this complication is very small.

The most important genital complication was loss of sexual function in the male, a subject fully discussed by Professor Goligher (1951) at a meeting of this Section. The same criteria have been applied as in his series, selecting patients for study who were under 60 years of age at operation, performed at least six months previously, and who prior to operation enjoyed an active sex life. So far we have only been able to interview a small series of 15 such patients and found potency in 60% and capability of full intercourse in 40%, figures lower than those given by Goligher.

In some the ability to have erections returned quite suddenly and in 2 cases occurred after a period of sixteen months. Nevertheless it is true that impotence may cause greater distress than the presence of a colostomy. There is no known way of avoiding this complication and many of these patients have suffered no significant urinary difficulties. Conversely, however, all those having severe urinary difficulties were impotent. It does seem that local trauma in the pelvic dissection is the major causative factor of this complication.

Difficulty with micturition is a common complication of excision of the rectum, and the immediate management of the bladder after operation is important but opinions vary from catheterization when necessary to the routine use of a catheter for five to seven days.

Figures from the Memorial Hospital, New York, by Marshall *et al.* (1946) showed that the perineal and abdomino-perineal excisions of the rectum had comparable post-operative urinary difficulties, 40–50% having no trouble, 28% severe trouble, 9% trouble for more than three months and 5% requiring further surgery. The abdominal dissection did not add materially to this hazard produced by the perineal dissection.

In the Gordon Hospital cases investigated, no significant urinary difficulty—meaning a catheter for less than a week—was found in 63% of males and 81% of females undergoing abdomino-perineal excision of the rectum (Table II). Levin and Ogden (1956) of New Orleans, recorded a series of 175 such cases with urinary dysfunction in 23%. A small series of anterior resections of the rectum showed figures of 82% males and 92% females having no urinary difficulty, and in this operation, although the posterior mobilization may be extensive, the anterior dissection is less and the rectal "cushion" still supports the bladder base.

It is true that a few males will pass urine without difficulty after excision of the rectum but since the great majority will not, it is an accepted principle of management to use a catheter in the early post-operative phase. An indwelling Foley catheter is used, the bladder emptied four-hourly, and the catheter kept in for five days. It is reinserted for further equal periods of time if micturition is not established or a large residual urine exists.

With the female, intermittent catheterization four- to six-hourly proves most efficient; it is clean and enables residual urine to be easily checked. It is important to watch for high residual urine.

Admittedly most cases got a urinary infection, the predominant organisms being *B. coli* and *Strep. fæcalis*, but this was readily controlled by the numerous antibiotics available,

all of which appear to have been used. Only occasionally has a persistent troublesome infection arisen which required bladder washouts using oxycyanide of mercury or Flavazole solutions, with effect. Urethral stricture was only seen twice, one case going into acute retention and the other producing vesical calculi. One Foley catheter became incarcerated and could only be extracted under anæsthetic. 3 cases of pyelonephritis were seen, 2 being chronic and for which a nephrectomy was performed.



FIG. 1.—Three large vesical calculi following prostatectomy and abdomino-perineal excision of rectum.

Calculus formation occurred in 4 cases, and calculi were removed by lithotrite or by open operation, as in Fig. 1. In 1 case failure with the lithotrite led to open operation. It was then obvious that a deep posterior recess was present due to sagging backwards of the bladder and that only by a very steep Trendelenburg position would the lithotrite ever have caught the stone.

Division of the ureter was seen in 4 cases, twice deliberately and twice accidentally, and on each occasion was then ligated. An intravenous pyelogram of such a case showed the gross hydronephrosis produced by the ligation. Simple suture of a ureter is very unsatisfactory (Graham and Goligher, 1954) and fistula is apt to follow simple ligation. Re-implantation into the bladder would appear to be the best approach and Begg and Dennehy (1953) suggest that re-implantation through the original intramural channel is most satisfactory, if technically feasible.

Table III shows the number of injuries to the genito-urinary tract. It was often difficult and tedious to close a vesico-perineal fistula and a typical case was operated upon twice via the perineum and twice via the bladder to effect closure.

Unilateral hydronephrosis, although suggesting ureteric damage from the operation, may be due to ureteric reflux in association with chronic prostatic obstruction.

The prostate has some influence on urinary difficulty after operation as shown in the series of cases reported by Watson and Williams (1952). In the presence of prostatic symptoms it does not seem justifiable to delay an operation for cancer of the rectum to remove the prostate and if the prostate is removed at the same time there is a higher risk of fistula, abscess or incontinence (Table IV).

Perurethral resection seems a very satisfactory form of treatment if urinary difficulty persists after operation, and Emmett (1957) of the Mayo Clinic was advocating this procedure for any such case as early as two weeks after operation. It is of interest that a female case of complete retention up to twenty-one days after operation was cured just by cystoscopy.

The cause of the difficulty after operation is usually mechanical in origin. Only 2 cases in this series would fall into the pelvic nerve, neurogenic bladder group described by Mr. Williams, and a possible other case was found early in the series, who has since died. A cystogram of a neurogenic bladder showed the typical funnel-neck appearance.

The major mechanical factor is the lack of pelvic supporting tissue after removing the rectum, and improvement in bladder function over the weeks appears to be a reflection of the healing of the posterior, or perineal, wound. In the female the uterus and vagina act as firmer supports for the bladder, provided childbirth has not caused undue laxity of the ligaments.

After removing the rectum the prostate has considerable mobility and by a study of a post-mortem case the prostate and bladder base were found to move almost 5 cm. backwards, which may well interfere with the mechanical efficiency of the external sphincter. Stripping of the peritoneum from the back of the bladder also allows a posterior cystocele to form and pre- and post-operative films showed this movement of the posterior bladder wall to be again about 5 cm.

Marshall *et al.* (1946) recorded a case with urinary difficulty treated by perurethral resection with resulting incontinence. This was cured by firm pressure in the perineum, not constricting the urethra but restoring normal anatomical position. This led them to do a ventrosuspension on a similar case, stitching bladder neck and prostate to pubis with success.

Cystometry on a series of Gordon Hospital patients showed that there was usually no disturbance of detrusor function even in the presence of urinary difficulty; when the rare neurogenic bladder resulted from operation it was quite easily detected by the absence of bladder sensation, its large volume and its steadily rising pressure as the bladder distended

Hence it would appear that when urinary dysfunction appears it is the mechanical disadvantages following the operation which are generally responsible. It would be of interest to know the incidence of bladder dysfunction in relation to tube drainage or packing of the perineal wound.

REFERENCES

BEGG, R. C., and DENNEHY, P. J. (1953) *Brit. J. Surg.*, **40,** 596.
EMMETT, J. L. (1957) *Surg. Clin. N. Amer.*, **37,** 4.
GOLIGHER, J. C. (1951) *Proc. R. Soc. Med.*, **44,** 824.
GRAHAM, J. W., and GOLIGHER, J. C. (1954) *Brit. J. Surg.*, **42,** 151.
LEVIN, I. A., and OGDEN, W. W. (1956) *Amer. J. Gastro-Ent.*, **25,** 463.
MARSHALL, V. F., POLLACK, R. S., and MILLER, C. (1946) *J. Urol.*, **55,** 409.
WATSON, P. C., and WILLIAMS, D. I. (1952) *Brit. J. Surg.*, **40,** 19.

**Mr. H. Gordon Ungley:** *Perineal Wound*

In a few cases where the perineal wound appeared to be granulating slowly or where dark, bloody discharge persisted, the perineum should be carefully inspected in the operating theatre, perhaps ten to fourteen days after the operation.

On the operating table, with good lighting, one can see the whole depth of the wound and often evacuate a clot of blood or loculus of fluid.

**Professor J. C. Goligher:**

I should like to comment on two points raised by Mr. Ramsay:

(1) *Management of Perineal Wound by Underwater-seal Drain.*—If one could avoid the large pelvic cavity and open perineal wound after abdomino-perineal excision the operation would be robbed of a great deal of its discomfort and the convalescence considerably shortened. When I first started in civilian practice after the War I did attempt to do this in two ways. In a few cases I closed the perineal wound completely, relying on a buried pack of alginate gauze (an absorbable hæmostatic) to control bleeding and fill the cavity, but the results were not satisfactory. In some other cases I also sutured the perineal wound *in toto* but left the pelvic peritoneum unstitched so that the small gut filled the pelvic cavity. Despite favourable reports of this method from Bacon and Babcock I had so much trouble with paralytic ileus that I had to cease using the method. As a result of these experiences I came reluctantly to the conclusion that the only reliable method of managing the perineal wound was to leave it partially open and to rely on granulations to fill it. In carrying out this I always leave the middle third of the wound unstitched for periodic digital exploration throughout the period of convalescence, to guard against the development of an hour-glass constriction of the wound cavity.

However, in the last nine months or so at the instigation of my senior assistant, Mr. A. V. Pollock, I have returned to the method of primary suture. Though I cannot yet make a detailed report, some comments on our experiences may be of interest. The wound is tightly closed round a stout rubber tube which is connected to an underwater-seal and retained in position for about a week. On removal, the pelvic cavity is not irrigated but a sterile outer dressing is applied as required. Antibiotic cover is given with penicillin and streptomycin. The method is popular with the nursing staff because of the reduction in the dressings required in the first post-operative days and subsequently. The patients find it extremely comfortable; 2 or 3 have developed troublesome infection in the wound cavity, usually superimposed on retained clots, but this has been easily dealt with by laying the wound widely open. The complication that one might apprehend is the development of a persistent sinus. We have had some of these which have been rather a disappointment, the wound continuing to discharge serous fluid or closing and then bursting open at a later date. But in time some of these sinuses have closed spontaneously. In conclusion I would say that I have an open mind as to the value of the method till it has been tried further, but I hope to make a more full report in due course.

(2) *Hartmann's operation.*—At one stage I was fond of the extended version of this operation as a quick, shockless method of terminating an abdomino-perineal excision, but I found that the convalescence after it was slow due to poor drainage from the pelvic cavity through the anus. I was therefore interested to find that Mr. Ramsay had noted similar difficulties.

**Mr. C. Patrick Sames:**

For several years now I have practised almost complete closure of the perineal wound, having in a moderate-sized drainage tube. This is placed high up in the pelvis and the wound closed tightly around it, bringing the tube out at the anterior end; to the end of the tube I fix a long piece of Paul's rubber tubing, the end of which is tied in a knot (Fig. 1). This

has the advantage of keeping the patient *completely* dry and aids the nursing immensely. Every twenty-four hours a nurse cuts the knot off and drains the extravasated blood into a receiver, measuring the amount. I find that the tube can usually be shortened after three or four days and removed about the end of a week and the residual track quickly closes. There have been occasions, however, when this method has failed and when it does so it is usually at the posterior end of the wound towards the coccyx (which I never excise). I think this failure must be recognized and the treatment then abandoned by removal of all sutures, otherwise a skin bridge tends to form and the patient is left with two difficult sinuses. However, this failure is so infrequent as to justify attempts at primary closure in most cases.

Incidentally, this method of affixing Paul's tubing is applicable to any case where considerable drainage is anticipated in whatever field of surgery it may be.

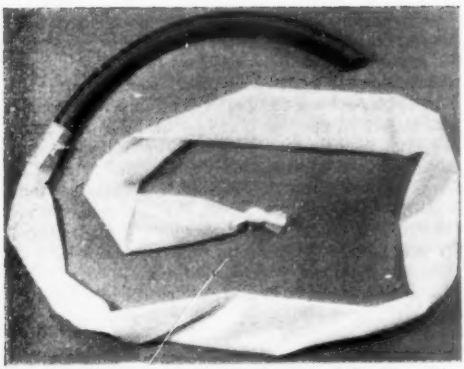


FIG. 1.—Drainage tube with length of Paul's rubber tubing attached for "closed drainage" of pelvic space.



FIG. 2.—Wad punch honed to make a circular cutting edge.

I should like to mention a method I have described in the *Lancet* (1958, i, 567) of bringing the colostomy out in an extraperitoneal fashion. A circle of skin and subcutaneous fat with external oblique aponeurosis is cut by the aid of a circular knife, fashioned from a simple wad-punch (purchased from the gunsmiths) and honed to a fine edge (Fig. 2). The internal oblique and transversalis muscles are split in the line of their fibres and with the finger a track is burrowed around the outside of the peritoneum to the raw surface posteriorly where the descending colon is taking attachment. Along this track the terminal bowel, previously crushed and divided, is guided by means of a large pair of Duval's forceps and the colostomy sutured to the skin by a primary mucocutaneous suture, as described by Butler (1952, *Proceedings*, **45**, 41).

This extraperitoneal fashioning of the colostomy is easier if undertaken before closure of the peritoneal floor. Care should be taken that there is no kinking of any residual mobile sigmoid between the lower end of the descending colon and the point where it begins to tunnel away beneath the peritoneum. This can be avoided by pulling a little more sigmoid through and, if necessary, resecting a further amount. Occasionally, a number of interrupted sutures may be required just where the descending colon commences on its new extraperitoneal course.

I have been practising this method for well over a year and can confidently recommend it. It would seem to be *the* answer to small bowel obstruction, occurring either from the lateral space (which now no longer exists), from loops of bowel becoming adherent to the under-surface of the colostomy where it passes through the abdominal wall, or from prolapsing of loops alongside.

# Section of Orthopædics

President—J. A. CHOLMELEY, F.R.C.S.

[*March* 22, 1958]

MEETING AT THE NORFOLK AND NORWICH HOSPITAL, NORWICH

## Sudeck's Atrophy and the Shoulder-hand Syndrome

By J. G. TAYLOR, F.R.C.S.

SUDECK'S atrophy and the shoulder-hand syndrome I believe to be related conditions. I shall discuss 10 cases of Sudeck's atrophy and 6 of the shoulder-hand syndrome. Though this is a small series it may be of interest to describe the clinical features and the results.

Since Sudeck's description of acute bone atrophy in 1900, most of the papers on the subject have come from Continental or American writers who have used a variety of descriptive titles. Many of those papers have emphasized the gravity of the prognosis in untreated cases, and have advocated operative treatment. A notable exception is the recent one by Plewes (1956) in which he shows that Sudeck's atrophy responds to conservative treatment if commenced within six weeks of the onset of symptoms.

The shoulder-hand syndrome was described by Steinbrocker in 1947, and in a more detailed study in 1948 (Steinbrocker *et al.*, 1948) he noted the relationship of this syndrome with Sudeck's atrophy. Sudeck's atrophy is an abnormal reaction of a limb, usually the extremity, to injury. It occurs most commonly after injury in the vicinity of the wrist or ankle joints and has been described as a complication of almost every form of trauma, often trivial. In this series fracture of the lower end of the radius was the usual preceding injury. There are four characteristic features of the condition: loss of motor function of an extremity, pain out of proportion to the causal lesion, vasomotor disturbance, and osteoporosis. After the causative injury there is usually early swelling with difficulty in maintaining finger or toe movements; there is increasing and persistent diffuse pain in the hand and wrist (or foot and ankle) which is not relieved by immobilization; the extremity becomes hot, red and puffy with loss of the normal fine creases in the skin; hyperæsthesia or paræsthesia may be present; there is increasing stiffness of hand or foot in which spasm seems to play a part. The rapidity of onset is variable—when the complication follows a Colles' fracture the symptoms may declare themselves soon after the injury or not become manifest until after the plaster is removed. Accompanying the acute stage of the disorder there is osteoporosis which is obvious at about six weeks in a comparative radiograph. The osteoporosis affects the cancellous tissue of the carpus, the lower ends of the radius and ulna and the extremities of the metacarpals and phalanges, and later their shafts (Fig. 1A). In the foot the corresponding bones are affected (Fig. 2A). The osteoporosis is at first patchy, giving a mottled appearance, but as it progresses it becomes more uniform, the trabecular structure of the bones becomes indistinct and the cortices are thinned.

The pain and loss of function persist or become worse, but the vasomotor phenomena tend to alter in character within the weeks and months after the initial injury so that the hot dry hand becomes cold and moist and the skin acquires a shiny atrophic appearance. Thickening may occur in the palmar fascia. Sometimes the dystrophy may be accompanied or followed by a homolateral painful, stiff shoulder.




FIG. 1A.—Comparative radiograph of hands twelve weeks after right Colles' fracture, showing typical appearance of early Sudeck's atrophy.




FIG. 1B.—Same patient two years after injury; there is still slight osteoporosis, though clinical recovery took only seven months.




FIG. 2A.—Sudeck's atrophy of the right foot, which followed a vascular disturbance three weeks after fracture of the tibia.



FIG. 2B.—The same case twenty months later, showing only partial recalcification.

In most cases the pain gradually lessens after a variable interval, the skin temperature and appearance return slowly to normal and movement improves. In my experience recovery with little or no disability is usual within a year to eighteen months. Grievous residual disability seems to be uncommon in this country, though it can follow the occasional severe case, especially when the patient acquires a fixed mental attitude of chronic invalidism. The osteoporosis may persist long after clinical recovery (Figs. 1B and 2B).

The shoulder-hand syndrome is a more extensive disability affecting the upper limb, in which a painful stiff shoulder is followed and accompanied by swelling, pain, stiffness and osteoporosis of the hand, similar to the changes described as Sudeck's atrophy. Sometimes the disability of the hand may precede that of the shoulder (Fig. 3). Like Sudeck's atrophy the shoulder-hand syndrome tends to fall into three stages. For the first few weeks or months there is a painful, stiff, tender shoulder and a hyperæmic swollen, painful hand with smooth taut skin and limited finger movement. Sometimes, however, the hand may be cold, purple and sweating. Thereafter the disorder may resolve, or diffuse pain in the shoulder and arm may persist with increasing atrophic changes, stiffness and osteoporosis of the hand, but decrease of swelling, and coldness instead of heat. The final stage is one of permanent disability from stiffness and sometimes persistent pain. The development and progress of the disorder from one stage to another are gradual, but it may resolve spontaneously during its course.

The shoulder-hand syndrome sometimes follows known injury such as a tear of the rotator cuff, but it has been observed also after myocardial infarction, hemiplegia, cervical nerve root irritation or herpes zoster. It is of interest that Osler in 1898 noted a "shoulder motor disability" after anginal attacks.

There is obvious similarity between Sudeck's atrophy and the shoulder-hand syndrome, and of the 9 cases of Sudeck's atrophy of the hand reviewed in this paper, some degree of pain or stiffness of the shoulder occurred in 5. It is tempting to support a theory of a common type of mechanism.



FIG. 3.—Shoulder-hand syndrome: photographs illustrating restriction of movement of right shoulder, and the swollen stiff right hand. (The normal left hand is shown for comparison.)

*Analysis of cases.*—The clinical material presenting Sudeck's atrophy: 10 cases. One patient had both hands affected with an eighteen month interval. The incidence of the condition is difficult to assess: during a four-year period when 8 of these cases were seen, the occurrence was 1:550 of all new cases of bone or joint injury attending that particular fracture clinic; Plewes mentions an incidence of 1:2,000 of accidents of all kinds attending the Luton Accident Service; on the other hand in the past three years I have seen only a single case in the Fracture Service of a hospital with a yearly attendance of 2,000 to 2,500 new patients; so there seems to be considerable geographical variation in the incidence.

Of the 10 cases in this series, 9 were in women and affected the hand, 8 after fracture near the wrist; one after a soft tissue injury and operation to the hand. A feature common to all these cases was early swelling and/or difficulty in maintaining finger movements. In the remaining case a man's foot was affected after what seemed to be a vascular complication following a fracture of his tibia; soon after being allowed up with a toe-to-groin plaster and crutches, he experienced severe pain and swelling of the foot; when the plaster was removed from the dorsum of the foot, petechial hæmorrhages were observed and the skin was dusky in colour, although the dorsalis pedis pulse was palpable. From then on the foot began to show the typical changes of Sudeck's atrophy (Figs. 2A and B).

6 cases of shoulder-hand syndrome were studied. In 4 the disorder was preceded by injury to the shoulder, in 1 a cardiac infarct preceded the condition, and in 1 no ætiological factor was found and the hand was affected before the shoulder.

*Treatment.*—The principles of treatment of Sudeck's atrophy and of shoulder-hand syndrome are the same. In this series of cases elevation was employed to reduce swelling of the hand and the patients were instructed to perform such finger, hand and shoulder movements as they could do themselves without increasing their pain. It was found that during the stage of spontaneous pain frequent physiotherapy in the form of heat and intensive active exercises aggravated the symptoms, and was therefore discontinued. When the phase of diminishing pain had been reached, wax baths, and active exercises became of value in restoring movement. This observation conforms with a number of authors, but recently Plewes has advocated early treatment by heat and active exercises using a specialized technique of hot wax and a polythene glove, followed by active exercises in a hot air cradle.

In 5 of the more severe hand cases and 2 shoulder-hand syndromes, repeated sympathetic ganglion block by local anæsthesia was carried out. In 1 hand case only was there convincing permanent improvement following the procedure—in the other cases the improvement each time was only temporary. Because of this temporary relief without permanent improvement, in the worst shoulder-hand case cervical sympathectomy was advised but refused by the patient who went on to suffer a permanent disability.

A short intensive course of cortisone or ACTH may be of value, and has been advocated. My experience, however, is limited to 2 cases of shoulder-hand syndrome and 1 of Sudeck's atrophy; in the former pain was relieved temporarily during each course of treatment but relapsed afterwards; in the latter, two short courses of cortisone were followed by great improvement and eventual recovery.

One shoulder-hand syndrome which had succeeded a cardiac infarct responded favourably to hydrocortisone injections into the shoulder.

*Results.*—The outcome in this series of cases of Sudeck's atrophy and shoulder-hand syndrome is considered to be reasonably satisfactory (Table I).

TABLE I.—RESULTS AND DISABILITY PERIODS IN SUDECK'S ATROPHY AND SHOULDER-HAND SYNDROME

| | End-result | | |
|---|---|---|---|
| | Normal function | Slight residual pain or impairment of function | Severe residual disability |
| 10 *cases of Sudeck's atrophy:* | | | |
| 8 following fracture near the wrist | 6 (average recovery period 10 months) | 1 at 10 months | 1 at 2 years plus |
| 1 following soft tissue injury to the hand | | 1 at 7 months | |
| 1 case in the foot after fracture of the tibia | | 1 at 2 years | |
| 6 *cases of shoulder-hand syndrome:* | | | |
| 4 following injury to the shoulder | 3 (average recovery period 6 months) | | 1 at 2 years plus |
| 1 following cardiac infarct | 1 | | |
| 1 of no discovered ætiology | | 1 at 2 years | |

In only 1 case of Sudeck's atrophy did severe disability persist, that of a woman with an unsatisfactory psychiatric background; 3 patients had slight disability; 6 had none and the average time for their full recovery was ten months.

Of the 6 patients with the shoulder-hand syndrome 4 made a complete recovery; 1 has slight residual stiffness but is at work and 1 had severe shoulder and hand disability after two years.

These cases are too few to be of statistical significance but they do suggest either that prognosis after relatively simple treatment is better than has been suggested by many Continental and American authors or that cases as severe as theirs are uncommon here.

It is probable, however, that in severe cases of shoulder-hand syndrome there is a greater risk of permanent disability than in Sudeck's atrophy of the hand alone which in most cases tends to spontaneous recovery. If in the shoulder-hand syndrome ACTH or cortisone therapy is ineffective and repeated sympathetic ganglion block only of temporary benefit, then early consideration to cervical sympathectomy should be given.

I am grateful to Professor Sir George Pickering, Dr. A. B. Pollard, Mr. J. Crawford Adams and Mr. J. C. Agerholm, for permission to include their patients in this series. I also wish to thank Dr. P. N. Cardew for the reproductions of the radiographs.

## REFERENCES

PLEWES, L. W. (1956) *J. Bone Jt. Surg.*, **38B**, 195.
STEINBROCKER, O. (1947) *Ann. Rheum. Dis.*, **6**, 80.
——, SPITZER, N., and FRIEDMAN, H. H. (1948) *Ann. intern. Med.*, **29**, 22.
SUDECK, P. (1900) *Arch. klin. Chir.*, **62**, 147.

## FOUR DEMONSTRATIONS by R. C. HOWARD, F.R.C.S.Ed.

### I.—"V" Arthrodesis of the Hip-joint

A diagrammatic film was shown of this operation describing the new posterior approach. The operation is designed for use in unilateral arthritis of the hip-joint. Deformities of the joint are corrected beforehand by doing an adductor tenotomy if necessary—this usually corrects the tendency to flexion deformity as well. External rotation deformities are corrected at the time of operation by doing a posterior capsulectomy.

The patient is operated on lying on his face and the hip-joint is approached by a postero-lateral incision. The joint is fixed by a long Smith-Petersen nail driven through the neck and head of the femur into the ilium without opening or dislocating the hip-joint. A 5-in. tibial graft is inserted through drill holes in the femur into the ischium and a plate is fixed to the outer end of the nail fixing the graft and preventing a fracture of the femur at the site of insertion of the graft. There is rigid three-dimensional fixation of the joint and the graft being in compression tends to unite and enlarges with time.

Patients are allowed up two weeks after the operation and knee movements are usually regained in four to six weeks, weight bearing being allowed at the end of this time.

The result of a personal series of 50 patients operated on between 1948 and 1954 showed a sound fusion in 94%.

### II.—Thoraco-scapular Arthrodesis (film)

This operation has been used three times for the rare condition of selective paralysis of the thoraco-scapular muscles. The scapula is fixed to the posterior thoracic cage by screwing three tibial strut grafts to the fourth, fifth and sixth ribs posteriorly. Sound bony union occurred within three months in all three operations.

### III.—Congenital Arteriovenous Aneurysm Involving the Shaft of the Femur

### IV.—The Complete Transplant of the 4th Metatarsal into the Soft Tissues of Rudimentary Thumbs, Followed by Flexor and Extensor Tendon Transposition

Four patients were shown where this operation had been done between seven and eight years ago in young children of between 3 and 7 years of age. Although all 4 children could waggle their thumbs, functionally and cosmetically the results were not as effective as pollicization of the index digital ray. The main feature of interest was that in one metatarsal the epiphysis was still growing after eight years, having increased the length of the metatarsal transplant by one centimetre.

## TWO DEMONSTRATIONS by G. K. MCKEE, F.R.C.S.

### I.—The Use and Development of an Artificial Hip-joint (film)

3 patients were shown in whom an artificial hip-joint, made up in Vinertia, had been inserted. They had all been relieved of pain and could walk without sticks, one as far as four miles. They all had a very satisfactory range of movement, both active and passive, so that they could sit down in comfort and one could actually bend down and touch his toes from a standing position. The development of the artificial hip-joint was described in three series of cases:

In the first series, 1951, stainless steel was used, but this was found to be an unsuitable material.

In the second series Vinertia with a Thompson-like blade for fixation of the femoral portion was employed, but this did not always obtain a very adequate hold at the time of operation. This model was used in 5 patients, 4 for failed acrylic prostheses with acetabular erosion and the other for osteoarthritis. They were all in a short plaster hip spica for six weeks. 1 patient died from acute dilatation of the stomach. The others have been greatly improved and the prosthesis has bonded on to the bone and become firmly fixed.

In the third series Vinertia was also used, the femoral portion being screwedin to the neck of the femur, and this has been much more satisfactory in that the apparatus can be firmly fixed in the bone at the initial operation and plaster fixation is not as a rule required. 22 patients have had this apparatus inserted between February 1957 and March 1958. This series shows, on the whole, very satisfactory results so far, although in some of the very old and feeble patients recovery of activity is not very good, but they are relieved of pain. There must, however, be adequate space to insert the apparatus between the great trochanter and acetabulum. Lack of sufficient space was encountered in one case of osteoarthritis with severe flexion deformity, in another case of failed acrylic prosthesis, where the prosthesis had eroded into the acetabulum and almost become embedded and in a third case of aseptic necrosis of the femoral head where the neck of the femur and great trochanter touched the acetabular rim.

**II.—Plastic Disc Supports**

A demonstration was given of direct application of polythene to a patient, made possible by the use of heat-resistant material, polyurethane, as described by Brennan (1954, 1955).

The design of the corset (developed at Norwich) was made to open in front, being controlled by two straps and buckles, and had very large cut-away openings at the sides, which not only give ventilation, but also make moulding of the support very much easier. The whole support could be made in under half an hour, including the application of the buckles.

Further details will be found in the following articles:

BRENNAN, J. B. (1954) *Lancet*, ii, 948.
——, (1955) *Lancet*, i, 841.
MCKEE, G. K. (1956) *Lancet*, i, 472.
—— (1957) *Med. Pr.*, **237**, 49.

## BOOK REVIEWS

**British Pharmacopœia 1958.** Published under the direction of the General Medical Council. (Pp. xxvi + 1012; illustrated. 63s.) London: The Pharmaceutical Press. 1958.

The British Pharmacopœia Commission are to be congratulated on the production of this new, ninth edition of the Pharmacopœia, published under the direction of the General Medical Council by the Pharmaceutical Press, which is official from September 1, 1958. Its preparation, taking into account the rapid development of the many new synthetic and biological substances which have been introduced since the last edition, is a formidable task, because the selection of appropriate substances for inclusion, requires considerable thought and judgment.

The members of the Commission, with their special knowledge in this sphere, ensure a high standard for this issue. It can be confidently recommended to all who need to refer to this admirably produced volume.

**Hospital Treatment of Alcoholism.** By Robert S. Wallerstein, M.D., and Associates. (Pp. x + 212; 42s.) London: Imago Publishing Co. Ltd. 1957.

This book evaluates the effects of four different techniques for treating alcoholism, a disease stated here to number 5 million victims in the U.S.A. and to be more untreatable than schizophrenia. In a Veterans Administration Hospital at Topeka, Kansas, 178 patients were given a three months' course with one of 4 different treatments, (1) antabuse, (2) group hypnotherapy, (3) psychoanalytically orientated group therapy, and (4) conditioned reflex (emetine) therapy. The percentage of improvement for the 4 techniques were respectively 53, 36, 26 and 24. The patients were subjected before, during and after treatment to Szondi psychological tests.

The editor seeks to evaluate for which type of patient one or other treatment is indicated or contra-indicated. This is, however, the most debatable part of the study. Despite the rather lukewarm approval accorded to antabuse, these results are likely to lead to a wider use of the drug or perhaps of some less toxic successor to it. This well-planned work, sponsored by Gardner Murphy and Karl Menninger, should be read by every worker in this field.

**The Neurologic and Psychiatric Aspects of the Disorders of Ageing.** By the Association for Research in Nervous and Mental Disease. Vol. XXXV. Editors: J. E. Moore, M.D., *et al.* (Pp. ix + 307; illustrated. 68s.) Baltimore: Williams & Wilkins Company. London: Baillière, Tindall & Cox. 1958.

This volume bears comparison with its distinguished predecessors. Its publication is timely, for there are some 14 million Americans of 65 and over and that number will have doubled in the next forty-five years. 6 out of 15 chapters are devoted to pathological changes in the brain and its blood vessels. Lancing, Weiss, Himwich, Kety, Andrew and Foley contribute in their special fields. The following are among some of the questions discussed: How far does heredity control the onset and severity of senility? Is there a phenomenon corresponding to Gowers' concept of abiotrophy or is senescence caused by toxic agents? Do some "senile" changes in the brain represent a defence reaction to such noxæ? How far are senile changes caused by vascular disease, and can "the bad plumbing" be prevented or improved? How far is senility accompanied by diminished oxidation of the brain cells? How far do those verging on 70 lose their "intelligence"?

These and many other questions are discussed with the aid of numerous tables, diagrams and illustrations. Pope has shown that senescence can be retarded in mammals (the rat) by uniting the older animal with a young one by means of a plastic operation. Clinicians too made notable contributions. Houston Merritt summed up well in several discussions, and Macdonald Critchley, the only English speaker, gave a comprehensive account of the clinical neurological aspects. A symposium on treatment showed how much can be done for old people despite the rather fatalistic attitude that too often prevails.

**Protides of the Biological Fluids.** Proceedings of the 5th Colloquium, Bruges 1957. Edited by H. Peeters. (Pp. viii + 260; illustrated. 45s.) London: Cleaver-Hume Press, Ltd. Amsterdam, etc.: Elsevier Publishing Co. 1958.

This volume records the proceedings of the 5th Congress on the Protides of Biological Fluids held in Bruges in 1957 and is mainly concerned with electrophoresis of the body

fluids. In his opening address, Tiselius emphasized that while informative qualitative results could be obtained with simple equipment, quantitative interpretation was likely to be more valuable. The thirty-nine papers which followed, contributed by authors mainly from Western Europe and Great Britain, were concerned with improvements in techniques such as automation, membrane filter electrophoresis, new methods of measurement as by polarography, new supporting media, as well as with the application of the technique to special problems such as copper binding in hæmocyanins and interaction of thyroxin with plasma proteins. A paper from California discussed the inhibition of proteolytic enzymes by plasma fraction while another from Germany claimed that malignant and benign tumours caused characteristic electrophoretic patterns. Especially interesting papers were on the geographical distribution of various hæmoglobins, on lipoproteins and on analbuminæmia. The Congress ended with a much-needed discussion on standardization of techniques.

**The Patient Speaks.** By Harold A. Abramson, M.D. (Pp. xxi + 239; $3.50.) New York: Vantage Press Inc. 1958.

A married woman of 32, with one daughter, had suffered since birth from asthma, hay fever and eczema, mostly during the pollen season. Her mother was a severe obsessional with a fear of germs and a washing mania. Subject to furious rages, she had beaten the patient mercilessly. The patient was completely dominated by her mother after puberty, although she had never experienced affectionate treatment from her. The mother told her that all "sex" was disgusting, advised criminal abortions for her daughters, having undergone one herself, and made such trouble between the patient and her husband that divorce was imminent. The patient was already adopting the same cruel behaviour to her own daughter. As the result of her worries, the patient's face was deformed by constant scratching.

The author, who came to psychoanalysis from biology (he wrote "Electrophoresis of Proteins", 1942), treated the patient with about 150 interviews in two years, after which she had ceased to scratch and was "99% recovered". She went through the pollen season without trouble. The patient has had a further 300 supportive treatments over nine years and is still free from symptoms. Her mother died the year after the eczema cleared up.

Dr. Abramson is to be congratulated on this account of the successful psychotherapy of a severely disturbed and allergic patient. Each interview was tape-recorded. The book demonstrates once again that psychotherapy is the chief weapon against allergic symptoms.

**Integrating the Approaches to Mental Disease.** Ed.: H. D. Kruse, M.D. (Pp. xvi + 393; 75s.) London, etc.: Cassell & Co. Ltd. 1957.

This book gives a verbatim account of two conferences held under the auspices of the Committee on Public Health of the New York Academy of Medicine in 1955–56. The purpose was to bring together leading members of the different disciplines which have a bearing on mental disorder. These workers were (1) psychotherapists, (2) experimental psychologists, (3) sociologists, and (4) "organicists", e.g. a neuropathologist, biochemist or geneticist. The psychogenic approach was ably expounded by Franz Alexander, while Whitehorn and Brosin as clinical psychiatrists chiefly held the balance between the exponents of the other disciplines concerned. E. Slater and D. Richter, the only English speakers, made valuable contributions in the spheres of genetics and biochemistry respectively. The conference was successful in that it forced experts in different fields to come together, and at times the level of discussion was very high, but in some respects the outcome was disappointing. The discussion related more to neurotic than to psychotic illness, and almost no reference was made to the physical treatments which have revolutionized psychiatry in the last generation. "I do not agree . . . that the problem of schizophrenia will be solved by the chemist", says a professor of sociology, p. 203. He considered that the paramount causal factor was social maladjustment and that this could be best remedied by the study of the behaviour of small social groups. In the light of recent developments he has perhaps been shown to be half right. In the English "therapeutic community" as the most up-to-date type of mental hospital is called, the chronic patients are losing their more crippling symptoms through not only "shock treatments" but through the use of chlorpromazine and its successors, while the sociologist, the psychotherapist and the clinical psychologist are co-operating equally in studying the best ways of rehabilitating the half-recovered patient, first in the hospital and, in many cases, later in the world outside.

**Cancer.** Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Vol. 3. (Pp. viii + 483 + 18; illustrated. 85s.) London: Butterworth. 1958.

Volume 3 contains chapters on the geography of cancer, occupational cancer, cancer education and detection, and on additional pathological aspects such as immunology, tissue culture, cancer in animals, and statistical investigations of human cancer. Once again, Mr. Ronald Raven is to be congratulated on the strength of the authoritative international team he has assembled. Of particular interest in the geographical section are the chapters on cancer of the lung in Africa, and on the peculiar features of cancer in India. The owner of these volumes is clearly going to have at his finger-tips a mass of information about all aspects of cancer which would otherwise be only laboriously acquired.

**Operative Surgery.** Edited by Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. In 8 volumes and index. (Volume 7: Breast, genito-urinary system: pp. xii + 273 + 3; illustrated. £5 10s.) London: Butterworth. 1958.

This 7th volume which deals with operations on the breast (42 pages) and on the genito-urinary system (272) pages, maintains the same high standards as its predecessors. One may perhaps mention especially Hanley's chapter on the numerous and varied operations for hydronephrosis, and Gummer's chapter on catheterization which is a perfect example of *multum in parvo*. As small points of criticism: in the breast section there is no indication that many people think routine sacrifice of the pectoralis major an unnecessary mutilation in the light of modern lymphatic anatomy and pathology; in removal of a duct papilloma, a radial incision is advised rather than the more cosmetic peri-areolar incision, through which also most fibro-adenomata can be removed; and there is no mention of operation for mamillary fistula. In the genito-urinary section, there is no mention under "Operation for varicocele" of the possibility of failure to relieve symptoms or of complications, and there is an unfortunate repeated misprint under operations for hydrocele, of "evulsion" of the tunica vaginalis instead of "eversion". But apart from minor criticisms such as these, the work can be said to pursue its majestic course.

**Operative Surgery.** Eds.: Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. In 8 volumes and index. Volume 8. Neurosurgery, Eyes, Ear, Nose & Throat. (Pp. xv + 238; illustrated; £5 10s.) London: Butterworth. 1958.

This final volume, dealing with neuro-surgical operations, eye operations, and operations on the ear, nose and throat, well illustrates some of the compromises forced on the editors in deciding on their public. In the section on neurological surgery, there is the following foreword: "The section . . . is not intended to be a comprehensive one as most of the major operations in this field should never be carried out except by persons with long training in the speciality." On the other hand, the other two sections describe such highly specialized operations as corneal grafting and the fenestration operation on the internal ear.

In spite of this, now that the work is completed and can be seen in perspective, your reviewer would like to re-echo his initial conclusion, that this is a greatly conceived and greatly executed work which will enhance the prestige of Britain.

**The Principles and Practice of Medicine.** Ed.: Sir Stanley Davidson, B.A.(Cantab.), M.D., F.R.C.P.Ed., F.R.C.P.Lond., M.D.Oslo. 4th ed. (Pp. xi + 1067; illustrated. 35s.) Edinburgh and London: E. and S. Livingstone Ltd. 1958.

That this textbook of medicine should have reached its fourth edition in a period of six years, is a measure of its value to students and practitioners. It maintains the high standard of previous editions. It is thoroughly up to date; every contributor is an expert in his field, and the Editor has overcome the common disadvantage of multiple contributors by close co-operation with the authors and careful scrutiny of every chapter. Although each subject is dealt with briefly and concisely, no essential point is omitted, either in problems of diagnosis or treatment.

**Eye Surgery.** By H. B. Stallard, M.B.E., M.A., M.D., F.R.C.S., Hon.LL.D. 3rd ed. (Pp. xii + 899; illustrated; 95s.) Bristol: John Wright & Sons Ltd. 1958.

Stallard's Eye Surgery continues to grow in size and stature. It is written with infinite care and although technique must of necessity form the substance of the text, the object of the operative procedure is never overlooked. Risks and complications are carefully assessed and prophylactic measures against mishaps are fully described. An indication of the hard work which has gone into the third edition may be gathered from the statement that 153 illustrations have been removed and 275 new illustrations added: all the drawings have been done by the author. The modern trends in ophthalmic surgery are included. The

chapters on anæsthesia and keratoplasty are largely rewritten but all through the book there is recognition of new work. The use of air in eye surgery, acrylic lens surgery, cyclo-anæmization, scleral overlap for detachment of the retina, and surgery of the vitreous are only a few chosen at random. The book is excellently produced and will be welcomed by practising eye surgeons of every seniority.

**The Art of Clinical Refraction.** By Theodore H. Whittington, M.D., M.R.C.P., D.O.M.S. (Pp. vi + 286 + vii; illustrated. 30s.) London: Oxford University Press. 1958.

There is nothing fundamentally new in this textbook and there are already several excellent treatises of a similar length on the subject of refraction. It is obvious that the author is an excellent teacher and there is a humane theme throughout his writing, stressing always that clinical refraction involves a doctor-patient relationship. But is this enough to justify a book of 286 pages? Whittington must have many grateful students in all parts of the world and they may care to read again what they learned under his tutelage when their potentialities were unlimited and their thoughts on a life in ophthalmology full of pleasurable expectancy. A beginner might profitably join this happy band. Nevertheless refraction is to the oculist what the multiplication tables are to the mathematician and there is a limit to variety in their presentation, "rough-hew them how we will".

**Behandlung Innerer Krankheiten.** Prof. Dr. Ferdinand Hoff. 8th ed. (Pp. xii + 733; DM. 59.50.) Stuttgart: Georg Thieme. 1958.

This is the eighth edition of a textbook produced by the director of the University Medical Clinic of Frankfurt and his colleagues. It is essentially a book on therapeutics and the authors have taken a lot of trouble to bring it up to date, so that most of the recently introduced drugs are discussed. There are, for example, very good sections on the new antibiotics and cytotoxic drugs. Marginal titles make it easy to follow the text and to look up various subjects. On the other hand, there are important differences in emphasis as compared with ideas of therapy in Britain. For example, the use of deoxycorticosterone in the treatment of Addison's disease is discussed in great detail, while cortisone and prednisone receive only a few lines. In the same way, the ganglion blocking agents receive scant attention in the section on hypertension. In the chemotherapy of tuberculosis much attention is given to the thiosemicarbazones, and the statement made that Conteben (thiacetazone) is particularly suitable in the prolonged treatment of chronic tuberculosis. There is a valuable appendix on poisoning with various drugs and also details of the various preparations mentioned (many of them trade names) with their prices.

**Burns—Pathology and Therapeutic Applications.** By Simon Sevitt, M.D., M.Sc., M.A., F.R.C.P.I., D.P.H. (Pp. xii + 364; illustrated. 37s. 6d.) London: Butterworth & Co. (Publishers) Ltd. 1957.

This is a well-produced volume, with clear photographs and diagrams, in keeping with the high standard of Messrs. Butterworth & Co.

It is not an easy book to read. The subject matter is given in great detail and several portions require a second reading. It is a book which should be studied by all those who attempt the treatment of burns, even by those who consider themselves experienced in this subject. It is filled with information, backed by experiment, illustrations and references.

The first three chapters give detailed analysis of the physical changes that occur when skin is heated at different temperatures, and reveal painstaking investigations. An understanding of the physical changes in burned tissues ensures a clearer appreciation of the after-effects of burning.

Classification of burns and the healing of burns are still something of a mystery outside Burns Units and Plastic Surgery Units. Chapter 4 on this aspect is to be commended to all those who receive burns cases, although Dr. Sevitt's statement that "the modern treatment of whole skin loss burns is immediate excision and skin grafting" is not wholly true.

The skin complications after burning are well stated, and there are two interesting chapters on infection and control of infection that should be broadcast to first-aid workers and nursing staffs.

The chapters on burns shock are complicated and make for slow reading but for better understanding of this complex subject. The account of the major redistribution of body fluids in burns shock makes it clear that these cases should not be treated haphazardly, but demand a more than ordinary knowledge of fluid replacement.

The remainder of the book deals with metabolic and endocrine responses to burning, together with the effect on liver, adrenals, and intestines.

Altogether, this is an admirable result of Dr. Sevitt's labour—a book full of facts clearly presented. It merits careful reading by all who have any contact with burns cases.

# Section of Otology with Section of Laryngology

JOINT SUMMER MEETING HELD AT THE ROYAL COLLEGE OF SURGEONS OF EDINBURGH

## OTOLOGICAL SESSION

Chairman—I. SIMSON HALL, F.R.C.P.Ed., F.R.C.S.Ed.
(President of the Section of Otology)

[*June* 27, 1958]

## DISCUSSION ON ACOUSTIC NEUROMA

**Dr. M. R. Dix and Dr. C. S. Hallpike[1]:**

*The Otoneurological Diagnosis of Tumours of the VIII Nerve*

In the course of the last twelve years it has been possible, through the good offices of our colleagues at Queen Square, to examine a large number of subjects suffering from tumours of, or affecting, the VIII nerve.

Although their total number has amounted to some 300, observations have been confined to a series of 95, in most of whom a full range of otoneurological tests was carried out, including tests for loudness recruitment, and in whom the presence of a tumour was later confirmed, either at operation or post mortem.

It is not the purpose of this communication to present any comprehensive catalogue of these findings. Instead, we have confined ourselves to a few familiar and practical themes concerned in the main with certain tests of cochlear and vestibular function, which lie very clearly within the province of the otologist and provide results of high diagnostic importance.

Our cases have been divided into the following two groups:

*Group I.*—Acoustic neurofibromata. The number of subjects in this group was 70.

*Group II.*—Other tumours arising within or invading the cerebello-pontine angle, and so involving the VIII nerve. The number of subjects in this group was 25.

*Cochlear Function*

*Hearing loss.*—Our first theme is the amount of the hearing loss in subjects with VIII nerve tumours. A review of the literature, especially some of the earlier papers, leaves the impression that the hearing loss is nearly always severe or complete, and indeed the belief still seems to be held in some quarters that, unless this is the case, the diagnosis of a tumour is doubtful (Cushing, 1917).

More recent publications have made it necessary to modify this view and Ireland (1949), in his series of 92 cases, reported normal audiometric findings in 5%. Edwards and Paterson (1951) also reported normal hearing in 2% of their 157 cases.

We have considered separately the findings in our two groups of subjects. Of the 70 subjects in Group I, with acoustic neurofibromata, there was a complaint of deafness in 91%. For the 25 subjects of Group II, however, this figure was only 72%. This difference was in agreement with the audiometric findings. Here, we have expressed the hearing loss as an average in decibels (db.) for the main speech frequencies, 500, 1,000 and 2,000 c/s. For Group I the average hearing loss was 53 db. For Group II, however, the hearing loss was only 42 db. These figures are summarized in Table I.

TABLE I.—HEARING IN 95 SUBJECTS WITH VERIFIED ANGLE TUMOURS

| | Group I<br>Acoustic neurofibromata | Group II<br>Other angle tumours |
|---|---|---|
| Complaint of deafness | 64 of 70 subjects (91%) | 18 of 25 subjects (72%) |
| Average pure tone loss for speech frequencies | 53 db. for 70 subjects | 42 db. for 25 subjects |

[1]From the Otological Research Unit, Medical Research Council, National Hospital, Queen Square, London, W.C.1.

Normal hearing does sometimes occur. In all of our 165 cases of verified acoustic neurofibromata, normal audiograms were found in 2 only. In the much smaller number of verified cases of other types of angle tumour, 63 in all, 4 showed normal hearing. It would seem, thus, that the degree of deafness in tumours affecting the VIII nerve is of some value in establishing the character of the tumour, the finding of slight or moderate deafness favouring the diagnosis of some variety of angle tumour other than an acoustic neurofibroma.

The 95 subjects included in Groups I and II amount to approximately one-third of our 300 cases. Their average hearing loss amounted to 48 decibels and in all 95 a measurable degree of hearing was preserved. It may be concluded that in at least one-third of our 300 cases some residual hearing remained.

*Loudness recruitment.*—This subject again cannot be considered apart from the hearing loss.

In Figs. 1 and 2 are shown the audiograms of cases in whom loudness recruitment tests

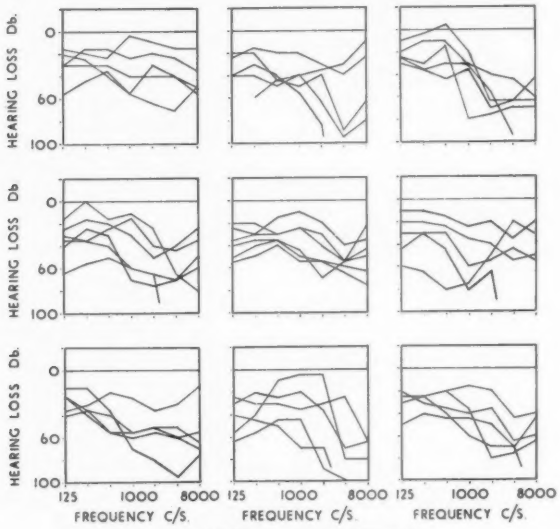



FIG. 1.—Angle tumours. Group I.

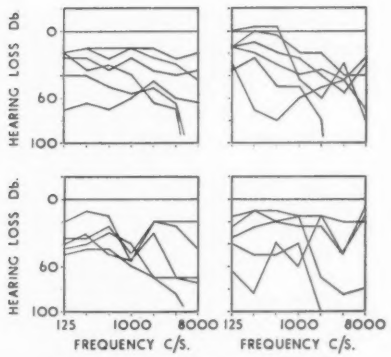



FIG. 2.—Angle tumours. Group II.

were carried out. In Fig. 1 are shown 47 cases of Group I. In Fig. 2 are shown 22 cases of Group II. It can be seen that in all of these cases quite useful hearing was present. In fact, in a significant proportion the hearing loss was surprisingly small.

The amount of this hearing is of some practical importance in relation to the practicability of tests for loudness recruitment; thus it is well known that Fowler (1949) attributed our findings of absence of loudness recruitment in VIII nerve tumours to severe deafness of the affected ear, resulting in a crossed response from the unaffected ear. The point is one which, of course, deserves careful consideration. It is generally agreed that the interaural attenuation for air-conducted sounds is of the order of 60 db. In our experience it nearly always exceeds this value. It follows that if recruitment tests were attempted in a case of unilateral deafness of the non-recruiting type, in which the hearing loss exceeded 60 db., then the result would certainly be, as Fowler states, a shadow curve, showing no recruitment, and comparable to the well-known shadow audiogram. In our subjects, however, the possibility of such an artifact does not exist.

In each of the 69 audiograms shown in Figs. 1 and 2 there was at least one frequency point at which the sensitivity difference between the two ears was less than 60 db.

In the vast majority of cases there were several such points, and at these points only, the recruitment tests were carried out.

It follows that in none of these 69 cases could the results have been confused by a cross-over effect. Needless to say, in unilateral deafness of the recruiting type, as found in Ménière's disease, loudness recruitment tests will still give valid readings at the higher intensities, and so can be used when the hearing loss exceeds 60 db. In fact, it may be said that loudness recruitment, when it does occur, is never an artifact. Hence, a positive recruitment test in any case of unilateral perceptive deafness, whatever its degree, makes very unlikely the diagnosis of an VIII nerve tumour.

The loudness recruitment tests are usually carried out at the following frequencies: 500, 1,000, 2,000 and 4,000 c/s.

In Fig. 3 are shown our results for the 47 cases of Group I. All of the curves start at a

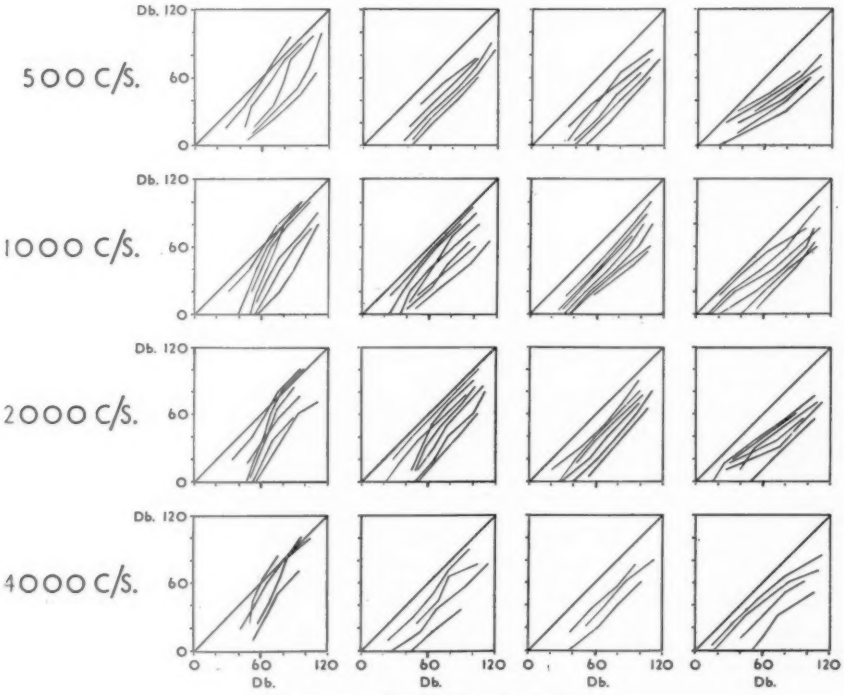



FIG. 3.—Angle tumours. Group I.

point to the left of the 60 db. mark; that is, in none did the hearing loss of the affected ear exceed 60 db. In most, the curves lie parallel to the normal equal loudness line, that is to say, loudness recruitment is completely absent. In a proportion, the curves show an

inclination upwards indicating partial loudness recruitment, but in a few only does it reach the normal equal loudness line, giving full recruitment. In quite a number of others the curve inclines downwards constituting the phenomenon of recruitment reversal, a phenomenon confined, so far as is known, to severe organic disorders of the cochlear nerve fibres.

In Fig. 4 are shown similar curves for the 22 cases in Group II. Again, nearly all the

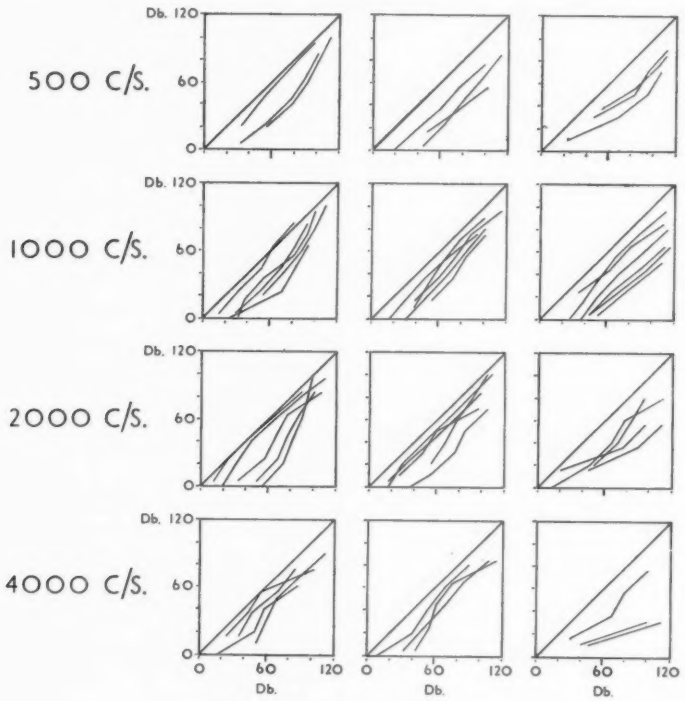



FIG. 4.—Angle tumours. Group II.

curves lie parallel to the normal equal loudness line, indicating the absence of loudness recruitment.

The number of cases in which full loudness recruitment was present at one or more frequencies was found to amount to some 10%. This requires explanation, and it may be recalled that we have explained it as being due to changes in the cochlear end-organ resulting from interference by tumour pressure with the cochlear blood supply (Dix and Hood, 1953). This argument was fortified by the finding in two such cases of the disappearance of loudness recruitment after the removal of the tumour.

Before leaving the subject of loudness recruitment, it would seem appropriate to consider the experiences of others. From a wide review of publications dealing with the diagnostic value of the tests it seems safe to say that since the demonstration (Dix *et al.*, 1948) that loudness recruitment was pathognomonic of end-organ disease, and was characteristically absent in VIII nerve tumours, the loudness recruitment test has continued to provide a most valuable means for the differentiation of cases of perceptive deafness into two classes: end-organ deafness and nerve fibre deafness. A complete list of other investigators who have substantiated these findings would be a long one, but the following seem particularly deserving of reference: Lundborg (1952), Möller and Nenzelius (1957) in Sweden; Kristensen and Jepsen (1952) and Thomsen (1955) in Denmark, Lüscher (1950) in Switzerland; Hahn (1954) in Italy, Zangemeister (1950), Jatho (1956) and Stenger (1956) in Germany; Ireland (1949) in Canada, and Riesco MacClure (1957) in Chile; and finally, Segal and Hociota (1957) in Roumania. In the United States, too, an increasing and formidable body of evidence has been accumulated by observers, including Saltzman (1949), Eby and Williams (1951), Jerger (1952), Schucknecht and Woellner (1955), Yantis (1955) and Goodman (1957).

Finally, Simonton (1956), in a paper published from the Mayo Clinic, reports findings very reminiscent of our own, in which he describes the disappearance of loudness recruitment following the removal of a small tumour. He agrees with us in attributing the loudness recruitment to end-organ damage, resulting from interference by the tumour with the cochlear blood supply.

In this country few contributions seem to have been made, and Denny (1955) has described the test as "not giving much assistance", the reason given being that absence of loudness recruitment in cases of VIII nerve tumour is not a constant finding. This we consider an unreasonable view. After all, very few diagnostic tests can be relied upon to give 100% results. Yet, in some respects, the diagnostic significance of the loudness recruitment test is as high as this. Thus, our own figures, well supported by others, show that the test is positive in 100% of cases of Ménière's disease, and negative in 90% of cases of VIII nerve tumours. A negative result, therefore, gives odds approaching the infinite against Ménière's disease. A positive result gives odds of 9 to 1 against a tumour. There can, we think, be few diagnostic tests which give results more decisive than this.

*Bone conduction.*—Another group of tests of great importance in the investigation of cochlear function is that of bone conduction. While the loudness recruitment test is indispensable in differentiating the two great categories of perceptive deafness, end-organ deafness and nerve fibre deafness, the diagnosis of perceptive deafness must first be established, and for this we are still vitally dependent upon the bone conduction tests.

Up to some ten years ago, references were to be found in the literature describing the occasional occurrence of true conductive deafness in cases of VIII nerve tumour. The tests were carried out in the classical manner with tuning forks, and evidence of satisfactory masking procedures was rarely provided.

We have ourselves (Dix and Hallpike, 1950) described 2 cases of VIII nerve tumours, examined some two years earlier, in whom we had encountered evidence of conductive deafness. In both of these cases the Rinne test gave what appeared to be true negative results.

We endeavoured to explain this conductive deafness in terms of a rather unusual albuminoid coagulum within the labyrinth. We used for our masking a hissing noise delivered to the unaffected ear from a speaking tube. This, at the time, was the best technique available, and we know now that its masking efficiency is inadequate. Since then electronically generated masking noises have been used, and for a number of years we have relied entirely on the narrow-band type of masking noise described by Hood (1957).

Since we have had this invaluable facility at our disposal, we seldom use the tuning forks for the evaluation of hearing by bone conduction, and have never seen a case of VIII nerve tumour in which there was any evidence of conductive deafness. So far as we know, the deafness of VIII nerve tumours is always of the perceptive type. We tell this story of our experiences, and of our change of views, since it illustrates in a manner which could not be bettered the extent to which efficient otoneurological diagnosis is dependent upon up-to-date audiological methods.

## Vestibular Function

We are in agreement with others that the early vestibular symptoms of VIII nerve tumours take the form of a sense of imbalance and unsteadiness of gait, and this was complained of in 73% of our 70 cases. Complaints of vertigo were only made in 49%. The term "vertigo" is not restricted to the paroxysmal kind of attack typical of Ménière's disease, and this we found to be of rare occurrence.

*Stance and gait.*—Tests for ataxia of stance and gait are important. These are carried out with the eyes closed and open. Abnormalities were present in 77% of our cases, though it must be added that their localizing value is by no means always clear cut.

*Spontaneous nystagmus.*—Examination for spontaneous nystagmus is of very great importance, and considerable experience is often needed to detect it in its early stages when it is often of high significance. The eyes must be observed under good diffuse lighting with the gaze directed straight ahead and deviated to left and right to points just within the limits of binocular vision. Spontaneous nystagmus was present in 81% of our cases in Group I as shown in Table II.

The findings have been considered in relation to the stage of development of the lesion, and it is fairly clear that nystagmus to the unaffected side is the first to appear, followed, as the tumour progresses, by nystagmus to the affected side. In some subjects we observed the development of this nystagmus over a period. When first detected it is of the first degree only, that is to say, it occurs only when the eyes are directed towards the unaffected side. Later it becomes of second degree, present, that is to say, also in the straight ahead position of gaze. At this stage it usually comes to be accompanied by first degree nystagmus towards the affected side. The findings seem to indicate that these two kinds of nystagmus, contra-

TABLE II.—SPONTANEOUS VESTIBULAR NYSTAGMUS IN 95 SUBJECTS WITH VERIFIED ANGLE TUMOURS

| Character of nystagmus | Group I Acoustic neurofibromata | Group II Other angle tumours |
|---|---|---|
| To contralateral side only .. .. | 20 (29%) | 9 (36%) |
| To ipsilateral side only .. .. | 1 (1%) | 0 |
| To both sides .. .. .. | 36 (51%) | 8 (32%) |
| Nystagmus absent .. .. .. | 13 (19%) | 8 (32%) |
| Total | 70 | 25 |

lateral and ipsilateral, are due to lesions of different anatomical structures, which are affected in a particular sequence. The structures whose derangement is responsible for the contralateral nystagmus are probably certain of the vestibular nuclear elements within the brain-stem. As to the structures which are concerned with the ipsilateral nystagmus, less can be said. The evidence, however, would seem to point to certain of the cerebellar elements.

*Positional nystagmus.*—Positional nystagmus is another physical sign of great importance and interest. It is, however, a specialized subject which cannot be included in the present contribution.

*Caloric tests.*—Lundborg (1952), in his extensive study of 300 proved acoustic neuromata, described the caloric as the most valuable of the tests of vestibular function. He stated that the results were abnormal in 84·2% of his subjects and normal in 15·8%. Revilla (1947) also, in his review of 145 cases, found 6·8% of normal caloric results.

Our own results have shown the caloric tests to give abnormal results in 100% of cases, and we regard the test, performed as we perform it, as indispensable.

The reason for the discrepancy between our findings and those of other workers arises, we feel sure, from differences in technique. Lundborg used 10 to 20 c.c. of water at either 27° C. or at 47° C., while Revilla used cold water only. We think it essential to use both cold and hot water at 30° C. and 44° C., as described by Fitzgerald and Hallpike (1942), and to interpret the results in accordance with certain principles which would seem to us to be reasonable and well founded. As explained in a number of publications since 1942, abnormalities in the pattern of the caloric test responses may take one of three possible forms; there may be a canal paresis; there may be a directional preponderance to the opposite side; or the two may be present in combination.

In Fig. 5 are shown these three possibilities, as they may be found in a tumour of the right

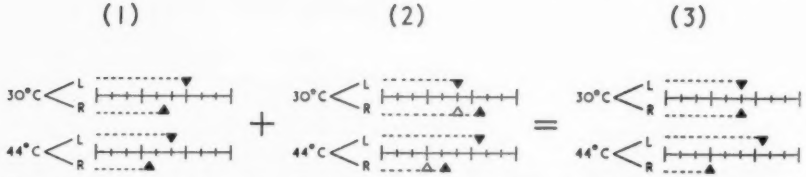



FIG. 5.—(1) Right canal paresis. Lesion of right canal elements. (2) Directional preponderance to left. Lesion of right tonus elements. (3) Combined lesions of right canal and right tonus elements.

VIII nerve. There may be right canal paresis (1), there may be a directional preponderance to the opposite side (2), or the two may be combined (3). The way the combined pattern (3) arises is easy to understand if we introduce into the directional preponderance pattern (2), a right canal paresis (1). The right cold response is then brought back to the point shown by the white triangle and the cold responses are thus made equal and apparently normal (3).

The right hot response again is brought back to the point shown by the white triangle, and the hot responses are thus widely separated (3). Consideration of these three patterns shows very clearly that cold stimulation alone will give the true answer only in cases of canal paresis (1). If there is a directional preponderance (2), then the cold responses would be misleading, since they would seem to show sensitivity loss of the left or unaffected labyrinth. Similarly with the combined pattern (3) the cold responses again give a misleading impression, namely, that the labyrinths react equally and normally.

The results of our caloric tests are shown in Table III. They are 100% abnormal. It may be seen that in 15 of our 95 cases exhibiting directional preponderance or a combined pattern, the results obtained with cold stimulation alone would have appeared entirely normal, or would have appeared to give a better response from the affected labyrinth. And

TABLE III.—ABNORMALITIES OF CALORIC RESPONSES IN 95 SUBJECTS WITH VERIFIED ANGLE TUMOURS

| | Group I Acoustic neurofibromata | Group II Other angle tumours |
|---|---|---|
| Canal paresis (total) .. .. | 58 (83%) | 8 (32%) |
| Canal paresis (partial) .. .. | 7 (10%) | 7 (28%) |
| Directional preponderance .. | 0 | 3 (12%) |
| Combined .. .. .. .. | 5 (7%) | 7 (28%) |
| Total | 70 | 25 |

this, we feel sure, is the explanation of normal caloric responses reported by Lundborg and others in VIII nerve tumours.

## DISCUSSION

We come now to certain wider problems connected with the otoneurological diagnosis of VIII nerve tumours. These we shall endeavour to outline in a series of questions which from time to time are put to us, directly or indirectly, by neurologists and otologists with practical interests in the clinical value of the modern diagnostic tests which we use.

The first question is: to what extent is the diagnostic evidence which they provide really indispensable? For instance, is it not true that in the majority of cases the demonstration of deafness will call for no special audiometric equipment, and that the simple observation of spontaneous nystagmus and the results of an ice-water caloric test will provide all we need to know of the vestibular dysfunction? If so, then such tests could be performed in any unspecialized aural clinic, and indeed the neurologist who is generally in charge of the case could well apply them himself and integrate their results with the neurological signs and symptoms which form an essential part of the clinical picture. Where, here, is the need for any highly specialized neuro-otological investigation? The question, arising as it does from prevailing clinical experience of these tumours with advanced deafness, spontaneous nystagmus and other neurological signs, is a perfectly reasonable one; and indeed, nothing has done more to discredit neuro-otology in the past than the unreasonable use in cases of this kind of over-elaborate diagnostic tests, in particular the rotational tests.

Our answer is that although these tumours are commonly presented for diagnosis in this advanced stage they should, if we look to the future, be seen much earlier, that is, in their otological stage, when their effects are for the most part limited to the VIII nerve elements. During this stage they will be detected by means of modern tests and by these alone.

The second question arises from what has just been said. Are we quite right in concluding that many of the tumours do pass through this purely otological stage? The affirmative answer, which we feel able to give, is based in part upon the evidence of histopathology, and in part upon clinical experience.

Let us consider first the neurofibromata of our Group I. The prevailing view of their pathogenesis, based chiefly upon the work of Henschen (1910, 1915) is that they arise from the neurilemmal portion of the vestibular nerve within the porus acusticus. Our own clinical data, being derived in the main from fairly advanced tumours, do not yield any decisive evidence as to the exact site of origin of the tumours. Nevertheless, some useful information is provided. Thus, in the 47 subjects whose audiograms are shown in Fig. 1 there was, as shown by these audiograms, a substantial preservation of cochlear function. In 83% of these, however, the caloric responses were completely abolished, and in another 17% they were severely reduced.

Partial loss of trigeminal function and other neurological disturbances were present in most of these cases in varying degrees. Nevertheless, the dominant note of the overall clinical picture is quite clearly indicative of a lesion having its maximum effect upon, and therefore originating in, the vestibular elements of the VIII nerve. We would expect, therefore, upon the evidence of these findings that all these tumours did, in fact, pass through an early otological stage in which their effects would be substantially limited to the VIII nerve, particularly its vestibular elements.

As regards the other tumours of our Group II, the story is a different one. Since the VIII nerve is not primarily involved, the VIII nerve signs are less in evidence than the neurological signs. Thus, good preservation of hearing is more likely to occur with incomplete loss of the caloric responses. Indeed, it is our experience of these tumours that some such unusual balance between the otological and neurological abnormalities often provides a useful key to their diagnosis. It need hardly be said that here again much depends upon the precise evaluation of cochlear and vestibular function by means of modern tests.

The next question is this: Granted the value of modern tests for the early diagnosis of these tumours, is the course of the surgical treatment greatly influenced thereby? This question may seem a peculiar one. Nevertheless, it is not without practical significance. Thus, in some subjects in whom we have made the diagnosis in advance of the appearance of any severe

neurological signs such as nystagmus, surgical treatment has been considered inadvisable; the opinion being held that in the absence of urgent indications such as papillœdema, the known post-operative morbidity makes it wiser to leave the tumour undisturbed. Now it is not really for us to provide the answer to this contention. Nevertheless, we feel bound to point out that it appears to be based upon the experience of the post-operative morbidity in advanced tumours. Experience of the post-operative morbidity in small tumours is unfortunately not yet widely available, but from such that we have, that is to say of tumours operated upon before the appearance of any evidence of brain-stem distortion, the post-operative morbidity is little more than that encountered following a section of the VIII nerve for Ménière's disease (Elliott and McKissock, 1954). The real difficulty at present is, we feel sure, that not enough of these cases are presented for diagnosis in their early, or otological, stage.

Having decided that the early diagnosis of these tumours is an essential factor in their effective surgical treatment and that this early diagnosis depends largely upon modern oto-neurological tests, we return finally to the question "What exactly are these tests, and what special technique and equipment do they require?" The subject needs no more than a swift review.

*The tests of vestibular function.*—Here, the caloric tests are of prime importance. Of their principles and practice no more need be said.

*The tests of cochlear function.*—For the establishment of the perceptive character of the deafness, reliable bone conduction tests are essential. These are impossible in many cases unless the correct masking procedure is employed. This involves the use of insert receivers and narrow-band masking noise, as described by Denes and Naunton (1952) and by Littler *et al.* (1952), and more recently developed by Hood.

*The loudness recruitment test.*—Here, again, special apparatus is required, of which the principles and their applications have been specified and fully described in a number of publications (Dix *et al.*, 1948; Dix and Hallpike, 1949; Hood, 1950; Dix and Hood, 1953; Hood, 1954).

*Test equipment.*—No serious difficulty would seem to arise in the case of the caloric tests. We have for years used a simple douche can and thermometer, but thermostatically controlled tanks make the work easier. These are readily obtainable and we warmly recommend their use.

More serious problems arise in connexion with the equipment needed for special tests of hearing. In our clinic practically all of the equipment we use has been designed to accord with certain theoretical principles, and has been constructed accordingly in our laboratories. In our hands it gives excellent results, and these provide the basis of a number of contributions published in the course of the last ten years relating to a variety of problems of cochlear and vestibular function in health and disease.

On the whole, our results have been substantiated; latterly, to an increasing extent by other workers. There is, however, no doubt that difficulties have arisen and it seems reasonable to suggest that they are attributable to some extent to the lack of the special equipment which we know to be such a vital necessity. Certainly we can say of any commercially available audiometers that in none is there yet provided any narrow-band masking for the performance of bone conduction tests; while facilities for loudness recruitment tests, when available at all, are nearly always quite inadequate.

Although the stress which we lay upon these various technical difficulties may seem very strong, we nevertheless consider it fully justified. If the otologist is to play his part, and play it well, in what we regard as an important and expanding field of work, he must have at his disposal up-to-date and efficient electro-acoustic and other equipment. There is no difficulty in specifying what this equipment should be, or its performance, and we hope that before long it will be properly standardized and made generally available.

## REFERENCES


Cushing, H. (1917) Tumours of the Nervus Acusticus and the Syndrome of the Cerebello-pontine angle. Philadelphia.

Denes, P., and Naunton, R. F. (1952) *Proc. R. Soc. Med.*, **45**, 790.

Denny, W. R. (1955) *J. Laryng.*, **69**, 608.

Dix, M. R., and Hallpike, C. S. (1949) *Proc. R. Soc. Med.*, **42**, 527.

——, —— (1950) *Proc. R. Soc. Med.*, **43**, 291.

——, ——, and Hood, J. D. (1948) *Proc. R. Soc. Med.*, **41**, 516.

——, and Hood, J. D. (1953) *J. Laryng.*, **67**, 343.

Eby, L. G., and Williams, H. L. (1951) *Laryngoscope, St. Louis*, **61**, 400.

Edwards, C. H., and Paterson, J. H. (1951) *Brain*, **74**, 144.

Elliott, F., and McKissock, W. (1954) *Lancet*, ii, 1189.

Fitzgerald, G., and Hallpike, C. S. (1942) *Brain*, **65**, 115.

Fowler, E. P. (1949) IV *Congr. int. Oto-rhino-laryng.*, **1**, 88.

GOODMAN, A. C. (1957) *Laryngoscope, St. Louis*, **67**, 987.
HAHN, R. (1954) *Minerva Otorinolaring*, **4**, 233.
HENSCHEN, F. (1910) Uber Geschwülste der Hinteren Schädelgrube. Jena.
—— (1915) *Arch. Psychiat. Nervenkr.*, **56**, 20.
HOOD, J. D. (1950) *Proc. R. Soc. Med.*, **43**, 1129.
—— (1954) *Acta med. belg.*, **1**, 27.
—— (1957) *Proc. R. Soc. Med.*, **50**, 689.
IRELAND, P. E. (1949) *Ann. Otol. Rhin. Laryng.*, **58**, 716.
JATHO, K. (1956) *Arch. Ohr.-, Nas.-, u. KehlkHeilk.*, **169**, 285.
JERGER, J. F. (1952) *Laryngoscope, St. Louis*, **62**, 1316.
KRISTENSEN, H. K., and JEPSEN, O. (1952) *Acta otolaryng., Stockh.*, **42**, 553.
LITTLER, T. S., KNIGHT, J. J., and STRANGE, P. H. (1952) *Proc. R. Soc. Med.*, **45**, 783.
LUNDBORG, J. (1952) *Acta otolaryng., Stockh.*, Suppl. 99.
LÜSCHER, E. (1950) *Proc. R. Soc. Med.*, **43**, 1116.
MÖLLER, F., and NENZELIUS, C. (1957) *Acta otolaryng., Stockh.*, **47**, 158.
REVILLA, A. G. (1947) *Bull. Johns Hopk. Hosp.*, **80**, 254.
RIESCO MACCLURE, J. J. (1957) *Rev. Otorinolaring., Santiago*, **17**, 6.
SALTZMAN, M. (1949) Clinical Audiology. New York.
SCHUCKNECHT, H. F., and WOELLNER, R. C. (1955) *J. Laryng.*, **69**, 75.
SEGAL, M., and HOCIOTA, D. (1957) *Oto-Rino-Laryng. Bucuresti*, 2/2 : 135.
SIMONTON, K. M. (1956) *Arch. Otolaryng., Chicago*, **63**, 262.
STENGER, H. H. (1956) *Arch. Ohr.-, Nas.-, u. KehlkHeilk.*, **169**, 285.
THOMSEN, K. A. (1955) *Acta otolaryng., Stockh.*, **45**, 544.
YANTIS, P. A. (1955) *Arch. Otolaryng., Chicago*, **62**, 625.
ZANGEMEISTER, H. E. (1950) *Acta otolaryng., Stockh.*, **38**, 484.

**Professor Norman M. Dott** (Department of Surgical Neurology, Edinburgh):

*Chronic Arachnoiditis and Hydrocephalus in the Surgical Management of Acoustic Tumours—A Plea for Early Operation*

*The late operation.*—The neurological surgeon has a special interest in the earliest possible diagnosis of the presence of an acoustic tumour and in the reference of the patient for neurosurgical treatment at this stage. In spite of the criteria for early otological diagnosis, the patient with an acoustic tumour is still apt to reach the brain surgeon in an advanced state of illness. In these advanced cases vision may be already permanently impaired from consecutive optic atrophy; the functions of balance and of muscular co-ordination may be permanently impaired by local softenings of cerebellar connexions and adjacent brain-stem, occasioned by increasing local tumour pressure; the patient is often seriously ill as a result of persistent vomiting, while the bronchial tree is at risk from aspiration due to the impairment of the swallowing mechanism. The surgical treatment of these advanced cases presents a difficult problem. If necessary, preliminary cerebrospinal fluid drainage can be established for a few days by ventricular catheterization, fluid and electrolyte balance corrected, and a preliminary or early post-operation tracheostomy may be provided. It is rarely possible to remove these large acoustic tumours completely without undue risk of damage to the pial blood vessels of those parts of the cerebellum and brain-stem that constitute the bed of the tumour and that become adherent to the capsule with long-standing large tumours. Similarly, the rootlets of the VII, IX, X and XI cranial nerves are at risk where they are stretched upon the capsule of one of these large tumours, if attempts are made to remove the capsule completely. Hence in these advanced cases one is often faced with the compromise of incomplete, subtotal removal of the tumour. By such means the surgical mortality can be held to 8% or 10% in these advanced cases; and morbidity in survivors can be minimized though not eliminated in respect of the permanent damage already established.

*Prognosis after late operation.*—The acoustic neuroma is a relatively slow-growing neoplasm; and with this factor, together with the decompression provided incidentally by the surgical approach, one might expect a long survival in the relatively satisfactory state achieved by subtotal extirpation. This expectation is realized in some 30% who survive this satisfactorily for ten to fifteen years.

Of the 60% who are less fortunate, about 20% have recurrent troubles from three to nine years after operation, due to further increase in volume of residual tumour fragments; but 40% have recurrent troubles in a few weeks to two years after operation from progressive hydrocephalic complications not caused by the physical size of residual tumour tissue. The cause of this serious complication is a subacute or chronic adhesive arachnoiditis affecting the basal subarachnoid cisterns and provoked by the proteinous transudate from residual tumour tissue into the surrounding cerebrospinal fluid.

*Chronic adhesive arachnoidits.*—A number of substances foreign to the leptomeninges may provoke inflammatory reaction in the lining membranes when they contaminate the

cerebrospinal fluid. Such are bacterial toxins, blood and the proteinous transudates from tumours. In respect of blood and of tumour transudates, there are probably degrees of individual allergic sensitivity. Thus proteinous transudate from an acoustic tumour may provoke in one individual a minimal arachnoiditis confined to the immediate vicinity of the tumour; and in another individual an extensive adhesive arachnoiditis of all the basal subarachnoid cisterns. Exceptionally in the most highly allergic, the arachnoiditis may overshadow the clinical syndrome when the tumour is still quite small. In such a case I have seen diabetes insipidus and mental changes from chiasmatic and interpeduncular arachnoiditis follow the initial unilateral deafness. The principal effect of arachnoiditis is to cause adhesive obstruction of the cerebrospinal fluid pathways. This is the cause of the arachnoidal cyst-like formation in the cerebello-pontine angle around the tumour; and, when the basal cisterns are more extensively blocked, of the chronic progressive hydrocephalus independent of the size of the tumour. It is in its earlier phases a reversible process; so that, if a tumour giving off such a transudate is completely removed at an early stage, the arachnoiditis may resolve, the fluid pathways may become re-established and the progressive hydrocephalus may regress.

It will be appreciated, therefore, that chronic progressive hydrocephalus may be a serious and an early complication in a substantial proportion of incompletely removed acoustic neuromas. The underlying adhesive arachnoiditis is too widespread and too inaccessible to permit surgical reopening of the fluid pathways. The best we can do for these patients is to direct the accumulating fluid elsewhere by implanting a silicone-rubber tube between the spinal theca and the peritoneal cavity. This may be effective for several years; and it can be repeated; but it is a precarious and imperfect substitute for a normal cerebrospinal fluid circulation.

The advanced case with a large acoustic neuroma—as contrasted with the early case with a small tumour—faces a long illness with increasing disability before operation, a more strenuous and complicated surgical experience with higher risks, severer post-operative residual disabilities, and about 40% recurrence risk from chronic progressive hydrocephalus in the first two years and 20% recurrence risk from further tumour growth during the fourth to the ninth years after operation.

*Early operation.*—The early case with a small tumour has no practical disability other than unilateral deafness before operation. The operation is little more than an anatomical exercise for the surgeon; and with much lower risks of mortality and morbidity for the patient. Complete removal can be achieved; and the prospects of subsequent trouble from chronic progressive hydrocephalus or from tumour regrowth disappear. Indeed the only residual disability, beyond the inevitable unilateral deafness, is facial paralysis in that majority of cases in which the facial nerve must be sacrificed to ensure total removal of tumour tissue from within the internal acoustic meatus. Even this facial paralysis need be but temporary; for with small tumours the proximal part of the facial nerve is easily identifiable, and the nerve can be reconstituted by an extra-petrous grafting procedure (*see* p. 900).

*The time to operate.*—Acoustic tumours should be dealt with by surgical removal as early as they can be diagnosed; and this signifies in the "otological stage" of diagnosis. In my experience corroboration can always be obtained by examination of the cerebrospinal fluid; for even the smallest tumours have caused a significant increase in its protein content.

The right time to remove an acoustic tumour is when it is no larger than a grain of wheat. I would, therefore, earnestly and strongly commend those accurate methods of diagnostic analysis of unilateral deafness described by Drs. M. R. Dix and C. S. Hallpike.

There is no justification for awaiting the advent of further complications—for as such we should regard ataxia, papilloedema, &c. This is emphasized by an understanding of those hydrocephalic complications that arise from contamination of the cerebrospinal fluid by the proteinous transudate that emanates from these tumours and from the smallest residual fragment of an incompletely removed tumour.

## Discussion

**Mr. William McKenzie** said that in his experience an acoustic neuroma was uncommon. In his own practice, he had found only two tumours of the cerebello-pontine angle, and of these, only one was an acoustic tumour, in over 200 cases of unilateral deafness. The remainder of his cases of acoustic neuroma had been referred to him at Maida Vale by his neurological colleagues, and the otological examination had served to confirm the diagnosis, but not to make it. The risk of operation had some influence on the diagnosis, because neurosurgeons were often reluctant to explore the posterior fossa unless the signs of a tumour were undeniable. In his hospital, Mr. Valentine Logue was unwilling to search for an acoustic tumour on the otological signs alone, and preferred to wait until the pathologist gave two reports of raised protein in the cerebrospinal fluid.

He had found it difficult to forecast the size or situation of the tumour by the character of the nystagmus, except of course that a first degree nystagmus to the opposite side suggested a small

tumour. The electrical recordings of the nystagmus had not proved as helpful as the differential caloric test of Fitzgerald, Cawthorne and Hallpike. He asked Dr. Dix what, in her opinion, was the limit of error in the differential caloric test. It seemed that the limit of error was at least enough to provide an occasional case of acoustic tumour where the result of the caloric test fell within normal limits.

**Dr. Dix** said that although, as Mr. McKenzie had pointed out, otologists would only rarely be called upon to make a positive diagnosis of an VIII nerve tumour, they would quite commonly be called upon to perform the equally important task of excluding one. Hence, it was important that they should be fully *au fait* with all aspects of modern diagnostic technique. As regards the limits of error of the caloric results, these had been studied statistically by Hallpike, Harrison and Slater (1951) and found to be reasonably small.

## REFERENCE

HALLPIKE, C. S., HARRISON, M. S., and SLATER, E. (1951) *Acta otolaryng., Stockh.*, **39**, 151.

**Mr. T. A. Clarke** congratulated Drs. Dix, Hallpike and Hood on their studies of recruitment and bone conduction audiometry; he thought it lamentable, however, that, with all the backing of the Medical Research Council behind them, they had not secured the commercial production of an audiometer satisfactory for these tests.

The vestibular caloric tests described were valuable, but he felt it necessary to repeat the comment he had made when the tests were first brought before the Section in 1943 (Cawthorne and Hallpike, *Proceedings*, **36**, 546). Caloric nystagmus had no sudden end point, it gradually faded out; in his experience there was a minimum of 20%–25% of subjects in which the end-point could not be stated within very wide limits. Importance was attached to the production of a pattern on the analysis of the responses; but so many manipulations were permissible (for hot/cold ratio, for canal paresis, for direct preponderance, for crossed and uncrossed lesions) that a pattern could be produced from any result. The greatest care must be taken, therefore, to exclude any observational or technical error.

**Mr. I. B. Thorburn** said that although he had been trying hard for a long time to spot the early case of VIII nerve tumour he reckoned that either it was an extremely rare condition or else he must have been missing them. While he was anxious to make an early diagnosis according to the criteria outlined by Dr. Hallpike and Dr. Dix, he wanted some corroborative evidence of intracranial upset. He thought it would help to clear the air if Professor Norman Dott would say whether he would be prepared to explore for an VIII nerve tumour on the strength of positive otological signs as outlined by Dr. Dix, where the patient had normal cerebrospinal fluid and negative findings on X-ray and neurological examination?

**Professor Dott,** replying to the discussion, said he appreciated the large amount of work involved in subjecting all cases of unilateral deafness, whose cause was not immediately apparent, to meticulous analytical tests. Nevertheless, only by this endeavour could we hope to diagnose a higher proportion of cases in the "otological stage"; and this was highly desirable in the patients' interests. He agreed with the reputed criteria of Mr. Valentine Logue in respect of surgery—positive otological findings together with a significant increase of protein in the cerebrospinal fluid. He felt sure he was speaking for most neurological surgeons in accepting those criteria. The risks of operation were very much less at this stage of the disease than they were later, when other neurological disturbances and radiological changes had made their appearance. The desirability of operation at the earliest stage compatible with a reasonably secure diagnosis seemed obvious.

Nevertheless, he, personally, would not consider that "positive" otological findings alone, without support from evidence of increased protein in the cerebrospinal fluid, furnished a sufficiently secure diagnosis to warrant intracranial surgery.

**Dr. J. D. Hood** said that the issues raised by Mr. Clarke on the subject of audiometry were very important. At the moment the position seemed unsatisfactory, since no commercial audiometer carried adequate facilities for the testing of loudness recruitment or bone conduction. Instead, the so-called clinical models provided a diversity of auxiliary tests which were for the most part of doubtful clinical value and involved so many switches and controls that the operation of these instruments had become disheartenningly complex. As a result, bone conduction and loudness recruitment tests were often inadequately or incorrectly carried out, and their great clinical value discredited.

In the last decade, advances in knowledge of the basic requirements in pure tone audiometry had been considerable, and could almost be said to have reached a stage of finality so that all that was really needed, or likely to be needed in the foreseeable future, could now be specified clearly and concisely. These requirements were quite simple. Apart from the conventional equipment for air conduction audiometry, the provision for recruitment tests called for little more than the introduction of an additional attenuator, while for bone conduction tests the narrow-band masking noises at specified frequencies referred to by Dr. Dix were needed.

With this equipment these tests would present no greater difficulty than the threshold audiograms, and the audiometer would be simplified considerably.

The manufacturers were not entirely to blame for the present state of affairs, since, so far as he knew, they had never received any clear statement of what otologists require. Until this statement was received and acted upon otologists must continue to be denied the use of these well-established tests of cochlear function.

# Facial Paralysis—Restitution by Extra-petrous Nerve Graft

By Professor NORMAN M. DOTT, C.B.E., F.R.C.S.Ed.
*Department of Surgical Neurology, Edinburgh*

THIS method provides restitution of continuity of the facial nerve between its origin from the brain-stem and the facial musculature.

*Field of applicability.*—It has been found applicable, under certain conditions, in the surgery of acoustic neuromas; and in cases of intra-petrous damage of the facial nerve—in which the lesion extends proximal to the geniculate ganglion—or when the petrous bone is so disorganized by disease or injury that the facial canal and nerve cannot be clearly identified. These conditions may pertain in comminuted fractures of the region, especially if they have been infected; and in tuberculous mastoiditis of childhood. The extra-petrous method becomes available as a "second string" in such cases when intra-petrous exploration of the facial nerve with a view to decompression or grafting has failed. In the surgery of acoustic neuromas it is applicable to those cases in which the facial nerve must be sacrificed in the interests of extirpating the tumour from the internal acoustic meatus; and in which the proximal part of the facial nerve can be identified adjacent to the brain-stem. These conditions are most likely to be realized in operating at an early stage of the acoustic neuroma syndrome, when the tumour is less than 15 mm. in diameter; though it has been employed successfully in a larger tumour.

*Methods available for relief of facial paralysis.*—I suggest that one can arrange methods of alleviation of facial paralysis in order of merit as follows: (1) Early spontaneous recovery without nerve degeneration and regeneration. (2) Late spontaneous recovery after regeneration, or procured by nerve decompression, neurolysis, nerve resection and suture, with or without nerve-grafting—either intra-petrous or extra-petrous. (3) Nerve substitution—as by hypoglosso-facial anastomosis. (4) Plastic procedures to minimize facial distortions. The first provides perfect recovery. The second provides a large measure of recovery of the facial motor mechanism—marred to some extent by "mixing of fibres" with some loss of individuality of movement and of tone of the several motor groupings of the face. The third provides recovery of tone but not of significant movement—so that the face at rest may be passable, but in action there is still hemiparalysis. The fourth provides similar conditions to the last—though less perfectly and at the expense of external facial scars. I would add that plastic procedures such as tarsorrhaphy may be of great value during the interval while awaiting a planned re-innervation.

The extra-petrous nerve graft method has recently been described and illustrated on my behalf by my friend, Dr. Karsten Kettel of Hillerod, Denmark (1958) and I will only summarize it briefly here.

### *Techniques of Extra-petrous Facial Nerve Graft*

The method is quite simple. The facial nerve is exposed in the cerebello-pontine angle by a unilateral cerebellar approach. There it is severed; and to the proximal stump a nerve graft some 15 cm. long is sutured. The graft is brought out through the craniotomy opening. A tunnel for the graft is made beneath the mastoid process in the plane between the sternomastoid muscle superficially and the splenius capitis deeply, extending forwards to the vicinity of the posterior surface of the parotid gland. The distal end of the graft is marked by clamping a silver clip across it, and it is thrust forward through the tunnel, some slack being coiled up at the distal end in the neighbourhood of the parotid gland. Ninety days are now allowed—the period calculated for nerve fibres to have tranversed the length of the graft and to have arrived at its distal end. The parotid region is now exposed, and, assisted by preliminary X-rays of the silver clip, that object is found and the distal few centimetres of the graft are gently unravelled. The facial nerve is now exposed at the stylomastoid foramen and cut there, leaving the distal stump protruding some 10 mm. from the posterior surface of the parotid gland. The graft is now brought to this stump. As much as convenient—usually several centimetres of the distal end of the graft—is removed. The second nerve suture is now completed between the distal end of the graft and the distal part of the facial nerve beyond the stylomastoid foramen. The entire intra-petrous section of the facial nerve is thus by-passed by the graft which runs behind and below the petrous bone.

In my 4 cases degenerated nerve graft was used. We used the sural cutaneous nerve from the back of the calf. It was exposed and ligatured in the popliteal fossa; and removed by a "vein stripper" technique for use ten or twelve days later. Degenerated nerve for

grafting was the fashion at the time I did these operations. I understand that peripheral nerve experts no longer consider preliminary degeneration important. The sural nerve is convenient in providing a length of 15 or 20 cm. without branches. Its sacrifice causes no material inconvenience. With its thick sheath it looks three times the diameter of the thinly sheathed intracranial facial nerve. I doubt, however, if the sural nerve contains a sufficient number of nerve fibres to match with those of the facial nerve. Our recoveries, allowing for the regeneration syndrome, have ranged from about 50% to 80% of normal function. They have been prompt, business-like recoveries—according to plan—and I think that with more nerve-fibre sheaths available a higher degree of recovery could be obtained. Recovery of tone has first been evident three to six months after the final, distal nerve suture; and recovery of movement some two months later. Only one point in technique requires special mention. In our first case we had removed an acoustic tumour; and having done so there was room to use a small curved needle for the nerve suture in the cerebello-pontine angle. Our later cases were instances of comminuted fractures of the petrous bone and the cerebello-pontine angle presented normal anatomy. Normal anatomy furnishes very little room for suture manipulations. We therefore constructed a fine needle holder (Fig. 1); in which we use a 7-mm. fine, straight, non-traumatic needle

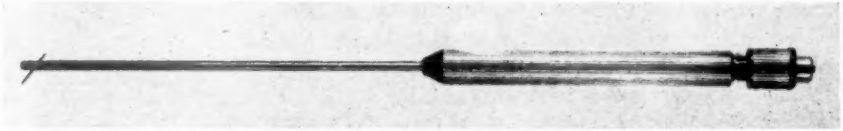


FIG. 1.—Special needle holder for use in cerebello-pontine angle.

mounted with fine silk. It is a pleasure to acknowledge the making of the needle holder—the handiwork of our former anæsthetist, Dr. Maxwell Brown. The little needles were kindly provided by Messrs. Ethicon, Edinburgh. In using these instruments it is convenient to transfix the facial nerve with the suture before dividing it about one millimetre distal to the suture.

## RESULTS

Our 4 cases are sufficiently illustrated by one of them (Fig. 2). The patient was a



At rest | Smile slightly. | Smile broadly. | Draw mouth to right (paralysed side).

FIG. 2.—Extra-petrous nerve graft for compound comminuted fracture with facial paralysis and disorganization of petrous bone. Patient ten years after treatment, carrying out facial movements as indicated.

Corporal of the Polish Army in Scotland in 1945, when he sustained an accidental crush fracture of the skull with a penetrating comminuted injury of the right mastoid region, facial paralysis and deafness. A mastoid operation to secure healing had been performed. There was reason to believe that the facial nerve was extensively destroyed, and to a level unlikely to be accessible from further intra-petrous exploration. An extra-petrous facial nerve graft from the cerebello-pontine angle was therefore carried out by my colleague, Mr. George L. Alexander, now of Bristol. It was done eleven months after injury and the second nerve suture three months later. Shortly after these events this Polish citizen was repatriated and disappeared from our ken behind the "Iron Curtain". However, when Poland raised that barrier to some extent last year, our patient was able—and was

so medically loyal as—to send me these photographs (Fig. 2) taken according to our instructions to bring out facial action. They show him ten years after treatment. He demonstrates at least 80% recovery and has really a very satisfactory result.

It may be noted that this long graft functioned in all 4 cases, 2 of them to about 50% of normal, which might be classed as fair results in terms of clinical facial paralysis—2 of them to about 80% of normal—very satisfactory results. No other means of restoring facial nerve continuity was available in these 4 cases.

I think it is best to provide re-innervation of the facial muscles not more than a year after paralysis, but fair results can be expected up to several years, especially when the muscles have been cared for by support to prevent over-stretching and by galvanism.

I suggest that research into the number of fibres in the facial nerve and the number of sheaths available in convenient grafts should be undertaken. It might well be better to use two sural nerves in parallel for the graft; or a larger nerve such as the external cutaneous nerve of thigh above Poupart's ligament.

REFERENCE

KETTEL, K. (1958) *Arch. Otolaryng., Chicago*, **67**, 65.

## LARYNGOLOGICAL SESSION

Chairman—R. J. CANN, M.S., F.R.C.S.
(President of the Section of Laryngology)

[*June* 28, 1958]

A DISCUSSION on **The Dysphonias and the Scope of Speech Therapy in Their Treatment** was opened by Mr. MAXWELL P. ELLIS and Mr. LEONARD WILLMORE.

Subsequent speakers were Mr. R. L. FLETT, Mr. I. G. ROBIN, Mr. R. G. MACBETH, Mr. J. ANGELL JAMES and Mrs. FLORENCE CAVANAGH.

Dr. MILES TAYLOR read a paper on **The Histochemical Characteristics of the Normal and Abnormal Nasal Respiratory Mucosa.** It was discussed by Mr. MAXWELL P. ELLIS and Mr. LIONEL TAYLOR.

The meeting will be reported in the *Journal of Laryngology*.

# Section of Orthopædics

President—J. A. CHOLMELEY, F.R.C.S.

[*April* 1, 1958]

## Hallux Valgus in Adolescents

### PRESIDENT'S ADDRESS

By J. A. CHOLMELEY, F.R.C.S.

*Royal National Orthopædic Hospital, Stanmore*

HALLUX VALGUS is a common deformity in adults, particularly women, and in children and adolescents its frequency is greater than many surgeons realize.

When an adult seeks medical advice about a hallux valgus it is usually on account of pain which may occur in the joint itself, over the bunion or under the metatarsal heads. When a child is referred on account of a hallux valgus the reason may be one of many—the appearance of the deformity, an increasing deformity, fear of increasing deformity, particularly when this has occurred to other members of the family, the spoiling of shoes or pain particularly over the bunion. Very often the child makes no complaint of pain.

Various operative procedures have been devised for the correction of hallux valgus in adults, such as Keller's or Mayo's arthroplasty and arthrodesis of the metatarsophalangeal joint of the great toe. Selection of the most suitable operation in an individual case is most important and even then the result is not by any means always an unqualified success. However, in an adult the metatarsophalangeal joint is often arthritic and in consequence we are dealing with poor articular material.

In a child or adolescent the problem is much more difficult as the metatarsophalangeal articular surfaces are usually normal and whatever treatment is carried out the joint should not be interfered with if possible. Various conservative measures have been described for the correction or control of hallux valgus. These are almost all useless. They include hallux valgus splints which, of necessity, can only be worn in bed and have to be removed when wearing shoes; toe pegs between the first and second toes which tend to push the second toe into valgus rather than correct the deformity of the first; exercises which mobilize the feet and toes but have little if any real effect on the deformity of the great toe.

If correction of the great toe deformity is necessary in any particular case in childhood or adolescence, operation is the only way to achieve this. Whatever operation is carried out the function of the foot must not be interfered with nor must the surfaces of the metatarsophalangeal joint be encroached upon or damaged.

Before embarking on any surgical procedure it is desirable to discover the underlying cause of the condition and to correct this first if possible. In hallux valgus, at least in childhood, the basic deformity is a metatarsus primus varus and correction of this is of prime importance. This has not always been considered to be the case, as witness the opinion expressed by Peabody (1931): "While it may safely be assumed that in some instances hallux valgus develops secondarily and inevitably from a congenital primus metatarsus varus, we believe that in the majority of cases the deformity at the great toe-joint is the important one." However, more recently the metatarsus primus varus has been considered the basic deformity. This opinion was expressed by Hawkins *et al.* (1945) in their paper on the correction of hallux valgus by metatarsal osteotomy. It has been argued that the varus of the first metatarsal is secondary to the hallux valgus. If this is so, then we must produce some adequate reasons for the lateral deviation of the great toe and this must incriminate the shoes. This, however, will not explain the cases of unilateral hallux valgus sometimes seen in children, but one cannot deny that some of the modern "casual" shoes worn by children have an undesirable influence on the progress of the deformity of the great toe and in town dwellers, at least, there has been an increase in the incidence of hallux valgus in adolescent girls.

It is important to define what constitutes a metatarsus primus varus. This is surprisingly difficult. According to Gray's Anatomy (1954) the metatarsal bone of the great toe lies parallel with the other metatarsals and has a limited degree of movement. Wood Jones (1949) shows a diagram of the foot from an 18 mm. human embryo where the angle between the first and second metatarsals is 13 degrees, and another of the bones of the foot of an Australian native woman where the divergence is 9 degrees. Ellis (1951) in his short preliminary paper on a method of correcting metatarsus primus varus by stapling, when discussing the prime metatarsal angle, refers to a control group average of 5·7 degrees and Mitchell *et al.* (1958) mention an angle of 10 degrees as being a metatarsus primus varus of abnormal extent. Hardy and Clapham (1951) give 8·5 degrees as the intermetatarsal angle in their control series and 13 degrees in feet with a hallux valgus deformity.

The next anatomical problem is the relative lengths of the metatarsals in the normal foot. Here again there is a divergence of opinion. Wood Jones (1949) states that Straus (1927) showed that the second metatarsal was, in his series, invariably the longest bone, whereas Morton (1935) categorically states that for the ideal foot function the heads of the first and second should be equidistant from the heel. Morton, however, also states that shortness of the first metatarsal can hardly be called a definite abnormality but he regards it as a defect. On the other hand, according to Wood Jones, Morton's defect is the accepted normal of all anatomists. If we take an average of the control figures of Ellis and Hardy and Clapham, we arrive at an intermetatarsal angle between the first and second shafts of 7·1 degrees and from the anatomists we should accept that the second metatarsal is usually the longest and projects beyond the first and third.

To correct a hallux valgus deformity, as I have already stated above, operative treatment is almost always required. To do this many procedures have been devised, some of which are applicable to the growing foot. That described by McBride (1928) consists of removal of the lateral sesamoid, excision of the prominent medial part of the metatarsal head and transplantation of the tendon of adductor hallucis into the metatarsal neck. This is largely a soft tissue operation. It does not correct the metatarsus primus varus and is probably only of use in the milder degrees of deformity. Most of the other operations, apart from arthroplasty or arthrodesis of the metatarsophalangeal joint, have been designed to correct the causative metatarsus primus varus.

Operations on bone and joint to correct the varus of the first metatarsal can be divided into three groups: those that can only be carried out during growth, those that should not be carried out during growth and those that can be carried out whether the epiphyses have fused or not. As a temporary measure removal of the prominent medial part of the head of the first metatarsal, combined with a basal osteotomy of the proximal phalanx of the great toe, sounds both simple and acceptable as the articular surfaces are not encroached upon. Unfortunately the results are by no means uniformly successful and may be most unsatisfactory.

Of the operations which depend on further growth of the metatarsals for correction of the deformity there is that described by Ellis (1951) in a preliminary report in which he stapled the lateral side of the epiphyseal plate at the base of the first metatarsal (Fig. 1).

Lapidus (1934) described an operation in which the medial cuneiform-first metatarsal joint is arthrodesed with simultaneous removal of a lateral wedge to correct the metatarsus primus varus; at the same time fusion of the adjacent surfaces of the first and second metatarsals is obtained by cancellous bone chips (Fig. 2). For this operation it is desirable that the basal epiphysis of the first metatarsal should already be fused.

The majority of other operations designed to correct adolescent hallux valgus include at least an osteotomy of the first metatarsal. Rocyn Jones (1948) described a specially designed osteotomy of the proximal part of the shaft of this metatarsal to correct the metatarsus primus varus (Fig. 3). Unfortunately relapse of the varus occurred in many cases, particularly where growth was not complete at the time of the operation. In fact if an osteotomy of the proximal end of the first metatarsal is to maintain correction of the varus deformity a bone graft must be inserted on the medial side and the first and second metatarsal heads kept in close contact. Bonney and Macnab (1952) suggested that a screw could be used to accomplish this. Stamm (1957) has described an operation fulfilling all these dicta; in this an osteotomy of the base of the first metatarsal is carried out and a graft obtained either from the prominent medial part of the metatarsal head or from a Keller arthroplasty is inserted in the medial side of the osteotomy to produce correction of the varus of the first metatarsal. To maintain this correction the tendon of adductor hallucis is transplanted through the neck of the first metatarsal (Fig. 4). In children and adolescents, even when the epiphyses have fused, the Keller arthroplasty should not be carried out as a stiff metatarsophalangeal joint is very liable to occur. In place of the adductor tendon transplantation the first and second metatarsal heads can be kept in

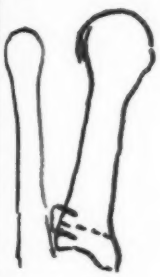


FIG. 1.—Ellis.

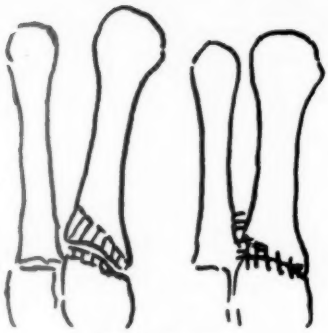


FIG. 2.—Lapidus.



FIG. 3.—Rocyn Jones.

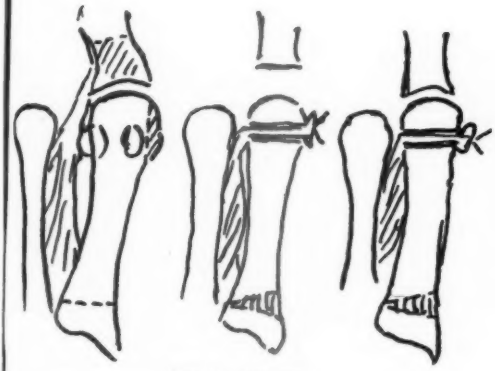


FIG. 4.—Stamm.

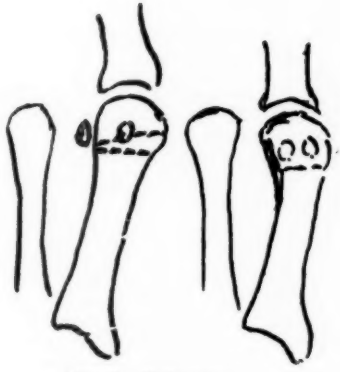


FIG. 5.—Hohmann.

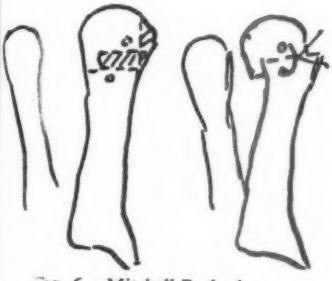


FIG. 6.—Mitchell-Peabody.

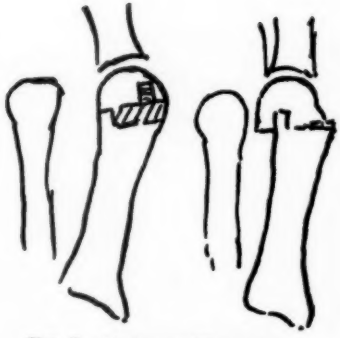


FIG. 7.—Hohmann-Thomasen.

close contact by means of nylon or catgut suture around the second metatarsal neck and through or round the neck of the first metatarsal.

Several years before the above operations on the first metatarsal shaft were described Hohmann (1924) described a transverse or oblique osteotomy of the neck of the first metatarsal, displacing the distal part laterally but without any internal fixation (Fig. 5). Peabody (1931) modified this operation by the formation of a lateral peg on the distal side of the osteotomy, displacing this laterally and fixing it by a catgut stitch through drill holes (Fig. 6). Hawkins *et al.* (1945) modified Peabody's operation by specifically removing a transverse section $\frac{1}{8}$ in. thick from the medial side of the metatarsal neck, leaving a lateral peg as did Peabody and fixing it by a catgut suture in the same way. A similar operation was described by Mitchell *et al.* (1958).

In 1952 Mygind of Copenhagen reported at a meeting of the Danish Orthopædic Association 535 cases of hallux valgus operated on by different methods and stated that the best results had been obtained by an oblique osteotomy of the first metatarsal close to the head, which was then displaced laterally and plantarwards on the shaft and kept in place by the hole and peg method devised by Thomasen (Fig. 7). Mygind also published in the following year a paper on this subject (1953). In 1953 Mortens of Copenhagen was working at the Royal National Orthopædic Hospital and introduced this operation to the staff of the hospital. Several cases of hallux valgus were operated on by this method but Cowie in a review of them was disappointed with many of the results due, in his opinion, to too early weight-bearing in plaster. Provided weight-bearing, even in plaster, is avoided for four weeks the results are much more uniformly satisfactory. The operation can also be carried out with safety in children in whom the epiphyses have not united and in adults where there is no gross radiological arthritis. Details of the operation consist of a transverse or oblique osteotomy of the neck of the first metatarsal and the formation of a lateral plantar peg on the proximal fragment with bone nibblers. A hole is then drilled on the medial side of the distal fragment and the peg pushed into it. The foot is immobilized in plaster for eight weeks, during the first four of which no weight bearing is permitted. For the final removal of the plaster the patient is readmitted to hospital for about a week when foot and toe mobilizing exercises are taught and the patient encouraged and trained in correct walking. X-rays taken at this time usually show singularly little callus formation, particularly in adults.

Certain objections can be levelled at this and the Mitchell-Peabody operations, such as the shortening of the first metatarsal, length of hospitalization and the long time in plaster. The first does not appear to be of any significance, particularly in children, and anatomically a long second metatarsal is not abnormal. The main advantage of the operation is that it corrects the metatarsus primus varus and the hallux valgus without interfering with the metatarsophalangeal joint.

In children and adolescents the operation of metatarsal osteotomy may be considered meddlesome surgery but what are the alternatives? These consist of doing nothing, even when the deformity is increasing or when pain is developing, ordering splints and exercises which are of little value, or prescribing shoes with a straight inner border wide enough to accommodate the broad forefoot and bunion, the surgeon knowing full well, if he is sincere with himself, that these shoes will rarely if ever be worn. In fact few young women will wear "sensible" shoes and few men, young or old, like the look of them.

## REFERENCES


Bonney, G. L. W., and Macnab, I. (1952) *J. Bone Jt. Surg.*, **34B**, 366.
Cowie, R. S. (1956) Personal communication.
Ellis, V. H. (1951) *J. Bone Jt. Surg.*, **33B**, 415.
Gray, H. (1954) Anatomy. 31st ed. Edited by T. B. Johnston and J. Whillis. London; p. 437.
Hardy, R. H., and Clapham, J. C. R. (1951) *J. Bone Jt. Surg.*, **33B**, 376.
Hawkins, F. B., Mitchell, C. L., and Hedrick, D. W. (1945) *J. Bone Jt. Surg.*, **27**, 387.
Hohmann, G. (1924) *Zbl. Chir.*, **51**, 230.
Jones, A. R. (1948) *Proc. R. Soc. Med.*, **41**, 392.
Jones, F. W. (1949) Structure and Function as Seen in the Foot. 2nd ed. London.
Lapidus, P. W. (1934) *Surg. Gynec. Obstet.*, **58**, 183.
McBride, E. D. (1928) *J. Bone Jt. Surg.*, **10**, 735.
Mitchell, C. L., Fleming, J. L., Allen, R., Glenney, C., and Sanford, G. A. (1958) *J. Bone Jt. Surg.*, **40A**, 41.
Morton, D. J. (1935) The Human Foot, its Evolution, Physiology and Functional Disorders. New York.
Mygind, H. B. (1952) *J. Bone Jt. Surg.*, **34B**, 529.
—— (1953) *Ugeskr. Læg.*, **115**, 236.
Peabody, C. W. (1931) *J. Bone Jt. Surg.*, **13**, 273.
Stamm, T. T. (1957) *Guy's Hosp. Rep.*, **106**, 273.
Straus, W. L. (1927) *Contr. Embryol. Carneg. Instn.*, **19**, 93.

# Section of Radiology

President—E. DUFF GRAY, M.A., M.D.

[*March* 21, 1958]

## DISCUSSION ON PITUITARY TUMOURS

**Mr. Harvey Jackson** (London):

*Surgical Aspects*

To quote the late Dr. Walter Dandy (1932), "Tumours of the Hypophysis are among the most frequent, the easiest to recognize and the most satisfactory to treat of all intracranial tumours".

Tumours of pituitary origin, in fact, represent something approaching 30% of all intracranial new growths (Love and Marshall, 1950).

*Sources of supply.*—Patients suffering from disorders of the pituitary reach the neurosurgeon by way of a number of different specialists. The explanation for this is simply that the several functions of the gland are influenced to varied degrees, and the outstanding feature in the individual case directs the mode of enquiry. Thus the general physician may be called upon because of increasing adiposity or glycosuria, the gynæcologist for amenorrhœa, the neurologist as visual disturbance or epilepsy develops, the ophthalmologist on account of visual deterioration and so on. The pædiatrician, the endocrinologist and even the psychiatrist, each has some part to play.

*Train of events.*—Tumours of the pituitary were first described in the last decade of the nineteenth century (Horrax *et al.*, 1955) but their clinical differentiation is of much more recent development. A somewhat circuitous course has taken place towards realization of outstanding clinical features of such diseases, amply illustrated by the way in which the interrelationship between amenorrhœa and pituitary dysfunction was fathomed. First, it became known that some girls in whom menstrual periods failed to appear in due course lost their vision. Deterioration of vision in such circumstances called for investigation which resulted in radiography of the skull. Some of the cases examined were found to have enlargement of the sella turcica, but this was not found invariably. Not until later was it realized that tumours above, or overlying, the sella turcica could bring about a like effect. Nowadays, with increasing knowledge about endocrine function the facts can be more fully determined.

### NATURE OF TUMOURS

The fact that both intrasellar and suprasellar growths at times give rise to like symptoms and signs calls for further elucidation. The inference is that while certain disturbances of function are related to the nature of the responsible lesion, others depend upon its site. We know that some kinds of pituitary adenoma may spread in various directions, and also that other forms of tumour are to be found either in, or above, the sella turcica, depending upon the original position of the parent cells.

Reflection on the embryology of the pituitary gland helps one to comprehend the varied nature of its tumour formations. The pituitary gland originates from two ectodermal outgrowths: the one from the primitive nasopharynx that forms the anterior or adenomatous structure; the other from the diencephalon that gives rise to the posterior portion, or pars nervosa. Between these two segments lies a cleft, the remnant of the nasopharyngeal pouch.

From the anterior portion of the gland, and from the epithelial lining of the cleft quite different kinds of neoplasm arise:

1) Tumours arising from the hypophysis.

2) Tumours arising from the hypophyseal stalk or duct.

*Tumours of the Hypophysis*

These are formed from the cellular components of the anterior lobe. As three different forms of adenomatous cell exist and these are recognizable as entities on their staining properties, so three different types of adenomatous tumour are to be met: adenoma of chromophobe, chromophil and basophil nature. These are, of course, pathologically innocent.

These three varieties of cell do not have the same propensity for new-growth formation. The chromophobe adenoma is about four times as common as the chromophilic type, whilst the basophil growth is very uncommon and usually of small, if not minute, proportions.

Not all tumours, however, conform with one or other type of cell; mixed cell types of adenoma do occur and moreover the largest pituitary tumours usually happen to be so constituted.

A proportion of the adenomatous growths do not remain within the sella, limited by the diaphragma sellæ, but may extend in one direction or another. Even though a tumour be restricted within the stretched diaphragma sellæ it may encroach upon the visual pathways, but once it extends beyond the roofing membrane further disorders arise in its course. Any suprasellar extension is of paramount importance from the points of view of treatment and prognosis.

Such extensions may track in any of the following ways:

(1) Upwards towards the hypothalamus, whence headache, drowsiness and diabetes insipidus ensue.

(2) Laterally towards the cavernous sinus, to give rise to proptosis, chemosis, engorgement of orbital tissues and possibly interference with ocular mobility.

(3) Upwards and forwards to encroach upon, or even penetrate, the frontal lobe. As the outcome of this, personality change may ensue with loss of initiative, memory defect, and possibly epilepsy.

(4) Into the middle fossa with involvement of the temporal lobe indicated by uncinate attacks, mental disturbance and visual field defects from implication of the optic tracts.

(5) Into the orbit by direct invasion via the optic canal, resulting in proptosis, interference with ocular movement and diplopia.

(6) In a basal or pharyngeal direction as a consequence of which cerebrospinal rhinorrhœa may occur.

(7) Backwards into the interpeduncular space and even along the clivus to below the tentorium.

To such a degree may the effects of extension pervade the clinical picture that the primary source of the tumour can escape recognition. For instance, the writer has seen a mass excised from the frontal lobe with the conviction that a radical operation had been performed until histological examination of excised tissue revealed the source of the growth to be the pituitary gland.

From the surgical point of view, the risks of operation are much increased once a tumour escapes the precincts of the sella. What would be a straightforward intervention regularly followed by rapid recovery is apt to assume hazardous potentialities and a high mortality.

An interesting feature of the pituitary adenoma is the possibility of sudden hæmorrhage within the capsule. It is a common belief that sudden and rapid deterioration of a patient's state, where he or she is the subject of an intracranial tumour, is to be explained on the basis of hæmorrhage into the tumour. In fact, such an event within brain tumours in general is not common, yet it is by no means exceptional in pituitary neoplasm. More than once has the writer reached hospital in the morning to operate on a case of pituitary adenoma, only to discover that the patient had succumbed overnight.

Another interesting experience was of a patient in whom sudden disturbance of visual acuity was followed by improvement within a few days. Mild pallor of the optic discs followed. This course of events was ascribed to disseminated sclerosis but proved to be due to a pituitary adenoma.

*Hypophyseal Duct Tumours*

A number of different terms are in common use for new growth which arises from the remnants of Rathke's pouch. These include: craniopharyngioma, hypophyseal duct tumour, suprasellar cyst, adamantinoma, Rathke pouch tumour. This is said to be the commonest non-gliomatous tumour of the brain, accounting for about 4% of all intracranial tumours (Love and Marshall, 1950).

As may be supposed from the various terms applied, this type of neoplasm may be found either within the sella, or above it.

Suprasellar tumours occur at any time of life, but are most frequent during the second decade. Their rate of growth varies greatly, 50% developing in a few months, but the other

50% last from one to thirty years (Love and Marshall, 1950). At each of two recent consecutive clinics an old patient reappeared after fifteen years: both have Rathke pouch tumours, both are still well and able to work. There seems to be little change in their physical states as judged in comparison with their prior condition.

*Adenocarcinoma of the pituitary.*—Malignant adenoma of the pituitary gland is rare; few authentic cases have been reported. The writer has met with one such case: A mass involving the sella, with destructive osteolytic changes on X-ray, was accompanied by dissemination involving vertebræ, pelvis, omentum and the liver. It was considered strange that the general state of the patient did not deteriorate so rapidly as one might suppose, possibly because of destruction of the gland. The condition was of over six years' standing.

*Pituitary abscess.*—From time to time a condition is found at operation wherein an encapsulated collection of material macroscopically resembling pus is evacuated from the region of the sella turcica. Thick, yellowish, pultaceous or creamy material is found. The underlying pathology is not of an inflammatory nature but neoplastic, appearing to be formed of degenerated tumour, either adenomatous or adamantinomatous in character. The contents are just structureless debris.

## Symptomatology

It is not intended to present an intimate citation of the manifestations exhibited by the various tumours of pituitary origin but it would not be opportune wholly to ignore the matter.

*Adenomas.*—As the cellular structure is varied, so is the influence on pituitary functions. Whereas the chromophobe adenoma tends to induce a picture of pituitary insufficiency, the chromophilic tumour gives rise to a state of hyperactivity of the gland.

The gland's normal functions being related to growth, sexual control, metabolism, and skin and hair development, features such as diminished sexual activity, diminution of hair growth with restricted necessity for shaving, and a tendency to lassitude attend diminished pituitary activity. The blood pressure is often low.

The chromophilic tumour influences growth, to produce gigantism or acromegaly according to whether the period of activity precedes or follows union of the epiphyses.

The basophil adenoma is responsible for some cases of Cushing's syndrome. Upon this there is no necessity to dilate for it plays little part in the main theme of the paper.

*Rathke pouch tumours* are not so intimately tied up with endocrine disorder as are the adenomata. Encroaching as they do upon the hypothalamus, they may well cause disorder of metabolism. Involvement of the tuber cinereum results in the state known as dystrophia adiposogenitalis, and interference within the supra-optic nucleus leads to diabetes insipidus.

An outstanding feature of the Rathke pouch tumour is its tendency to undergo calcification; an appearance results on X-ray that may be said to be pathognomonic. Perhaps 70 to 80% show calcific deposits (Fig. 1). Where these changes are not present it may be difficult to



Fig. 1.—Calcification in a Rathke pouch tumour.

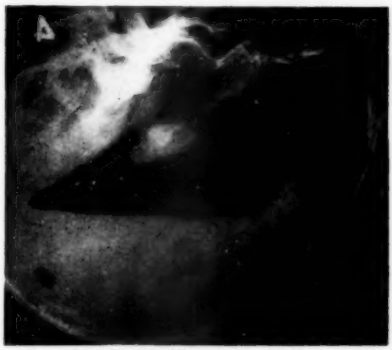



Fig. 2.—Gross dilatation of the anterior part of the third ventricle such as gives rise to visual disturbances comparable to those induced by pituitary tumour.

be sure whether alterations in the sella are due to an immediate tumour, or the outcome of dilatation of the third ventricle in relation to a generalized hydrocephalus. Indeed, differentiation between a suprasellar tumour and even a subtentorial lesion may require investigation by ventriculography (Fig. 2).

The basic symptomatology of the Rathke pouch tumour varies with the age of the patient. In early life, growth disturbance and increasing intracranial pressure engage attention. During the intermediate decades, endocrine and metabolic disorders are outstanding symptoms; in yet older patients, visual disturbance is usually the guide.

## Differential Diagnosis

Where surgery applies attention must be focused on interference with vision and/or disturbances of intracranial pressure. A number of pathologies other than new growth of pituitary origin need to be considered if avoidable errors are not to be made, and their differentiation from pituitary growth is attendant on clinical, radiographic and other investigations (Fig. 3). Of such pathological conditions may be mentioned the following:



Fig. 3.—Typical ballooned sella turcica as found in association with a pituitary adenoma.

Pituitary adenoma, Rathke pouch tumour, suprasellar meningioma, dermoid and epidermoid tumours, glioma of the optic chiasma, adenocarcinoma of the pituitary, metastatic carcinoma, aneurysm (especially of the anterior communicating artery), chiasmal arachnoiditis, chiasmal injury. It is not proposed that the establishment of each individual pathology should be subject to discussion. Suffice it to say that a pre-operative pathological diagnosis should be determinable in a large majority of cases.

## Treatment

It was Harvey Cushing's practice to operate on patients suspected of having a pituitary tumour only where vision was involved or obstruction to the cerebrospinal fluid pathways occurred (Henderson, 1939). I would suggest that it is not merely involvement of the visual tracts that determines the issue, rather is it progressive involvement, for one encounters a number of patients manifesting definitive visual field disorders who yet can carry on undisturbed and undisabled over many years without treatment. Quite recently the writer has encountered two cases of twenty-five years' standing, one with bitemporal hemianopia. In neither case does there appear to have been any deterioration of note.

It is not my intention to go into the various methods and routes of surgical intervention. What one wishes to convey is the necessity for surgery where a patient is progressively affected and the general health is of a quality that justifies the necessary procedure.

First of all, at the present time one does not operate for endocrine disorder alone.

Where surgery is indicated, it should be considered as a primary measure, not merely a subsidiary, applied only where irradiation has failed. My reasons for this decision are:

(*a*) Cystic tumours do not respond to irradiation. It is not possible on clinical or radiological data to say whether in a given case the actual lesion is cystic or solid.

(*b*) Tumours of Rathke pouch origin are not responsive to high voltage therapy. Therefore, where the nature of the tumour remains in doubt, only surgery is permissible.

(*c*) Series as reported by Horrax *et al.* show an unsatisfactory response to initial deep therapy, 58 out of 99 cases being inadequately responsive (Horrax *et al.*, 1955).

(*d*) High voltage therapy may have disastrous effects. This may be ascribable to technique and therefore avoidable.

My personal opinion is that operation should be given primary consideration where it applies, but that a course of teletherapy should follow. In support of this I would like to say that for the last twenty-five years it has been my practice to treat cases of adenoma of the pituitary in this way. During the early part of World War II deep therapy was not generally available to us. As a result, cases reappeared showing relatively early deterioration,

and it was only when what one considered normal procedure was again possible that more lasting recoveries ensued.

I should prefer to reserve primary irradiation for cases where the tumour has escaped beyond the sella, circumstances seriously affecting the mortality and morbidity of surgical intervention.

## REFERENCES

DANDY, W. E. (1932) Practice of Surgery. Edited by Dean Lewis. Hagerstown; **12,** 566.
HENDERSON, W. R. (1939) *Brit. J. Surg.*, **26,** 811.
HORRAX, G., SMEDAL, M. I., TRUMP, J. G., GRANKE, R. C., and WRIGHT, K. A. (1955) *New Engl. J. Med.*, **252,** 524.
LOVE, J. G., and MARSHALL, T. M. (1950) *Surg. Gynec. Obstet.*, **90,** 591.

**Mr. J. Jackson Richmond** (London):

### *The Role of Radiotherapy*

A brief historical survey of the treatment of pituitary tumours by irradiation during the past fifty years was outlined. The clinical response of pituitary adenomas in the early years was disappointing, which was not surprising in view of the inadequate facilities available and scanty knowledge of dosimetry compared to modern-day standards. With the high development of surgical technique, particularly through the intracranial approach by the Harvey Cushing school, such promising results followed that surgery became the accepted method of treatment. Although Cushing himself predicted that radiotherapy would come to be discarded in the treatment of chromophobe adenomas, Henderson (1939) in his most comprehensive monograph based on a review of Cushing's large series of cases revealed that the patients who had received post-operative X-ray therapy had a most significant percentage increase of the five-year periods without recurrences.

*Increasing use of radiotherapy.*—During the past twenty years many reports of series of cases of pituitary adenomas both chromophobe and chromophil have been published which clearly establish the relative radiosensitivity of these tumours. Certainly in several North American neurosurgical units the pendulum has swung to the opposite side in that these adenomas are treated by irradiation in the first instance and only those cases which prove refractory to the therapy or show signs of further visual impairment are subsequently explored.

*Hazards of radiotherapy.*—It was shown that tumour regression bore a definite relation to the dosage of radiation delivered to the tumour. In general, the higher the dosage the more impressive the immediate response, but unfortunately it is only in relatively recent years that a full appreciation of the vulnerability of the tissues of the central nervous system to ionizing radiations has come into clear focus. There can be little doubt that many patients have met with premature death as a direct result of irradiation damage to the neighbouring brain tissue, particularly to the hypothalamic region which is in immediate anatomical relation to the pituitary.

Unfortunately, irreversible effects can be produced by dosages of radiation not greatly in excess of those considered to be at a safe therapeutic level. In illustration, one unfortunate case in the series was quoted:

> A woman of 55 had a confirmed chromophobe adenoma partially excised and followed by X-ray treatment. For some unaccountable reason the dosage of X-rays prescribed was 4,500 r instead of the customary maximum level of 4,000 r in four weeks. The patient made satisfactory progress until one year later when she developed headache, associated with deterioration of vision. This progressed to drowsiness and disorientation when she was readmitted to the National Hospital, Queen Square, under the care of Dr. E. A. Carmichael and Mr. Wylie McKissock. It was thought that she might have arachnoiditis of the chiasmal region, and craniotomy was performed in an attempt to relieve this. The patient's condition deteriorated, however, and she died a few days later with hyperthermia and low blood pressure.
>
> Autopsy was performed by Dr. W. Blackwood and definite post-irradiation changes were demonstrated in the hypothalamus which could account for the patient's death. [Slides prepared by Dr. Blackwood were shown to illustrate the macroscopic and microscopic changes in the involved region of the brain.]

*Advantages of combined surgical and radiation treatment.*—In this country it is common practice to perform preliminary surgical exploration and partial excision of the adenoma. The advantages may be enumerated:

(1) This permits immediate decompression of the visual pathways. Permanent blindness may occur in a relatively short period of time in a proportion of cases which do not respond to primary irradiation.

(2) A direct assessment of the size and extent of the adenoma can be made. Excision of a large proportion of the tumour allows irradiation to be concentrated on a much smaller volume of tissue and permits standardization of the technique.

(3) Histological verification of the tumour can be obtained. It is well known that other conditions may simulate the "pituitary syndrome", e.g. a tumour in the posterior fossa causing dilatation of the third ventricle, a meningioma or glioma in relation to the clinoid processes, an aneurysm of the circle of Willis, a suprasellar cyst, or even a localized metastasis.

The disadvantage of surgery lies in the operative mortality which fortunately is now extremely low in the hands of experienced neurosurgeons.

### *Review of Personal Series of Cases*

A total of 220 patients who have received radiotherapy during the past fourteen years came under review and Table I indicates the various pathological groups. The average age of the patients was 43·1 years and the age range 17–70 years. There were 122 (55%) males and 98 (45%) females.

TABLE I.—PITUITARY TUMOURS: PATHOLOGICAL CLASSIFICATION

| | | |
|---|---|---|
| Chromophobe adenomas | Typical 145, "mixed" 20 | 165 |
| Eosinophil tumours (acromegaly) | | 16 |
| Pituitary basophilism (Cushing's syndrome) | | 9 |
| Craniopharyngiomas | | 11 |
| Carcinomas | | 7 |
| Unexplored (presumed chromophobe) | | 12 |
| | Total patients | 220 |

The chromophobe adenomas form the largest group in this series and the subsequent discussion will be confined mainly to these tumours. It is common to find a relatively high proportion of eosinophil tumours but it will be noticed that some of the chromophobe adenomas are labelled "mixed" cell tumours.

### *Delay in Diagnosis of Chromophobe Adenomas*

The life-history of these tumours usually extends over many years and if the accompanying degree of hypopituitarism is low then visual impairment alone brings the patient under investigation. Nevertheless it should be possible to refer a proportion of these cases for treatment at much earlier periods. This applies particularly to women for in this series no less than 41 female patients in a total complement of 78 women gave a history of early menopause. The average interval from the time of cessation of periods until presenting for treatment is calculated at 7·5 years. In women with unexplained amenorrhœa even a simple lateral radiograph of the skull may lead to the correct diagnosis in many instances.

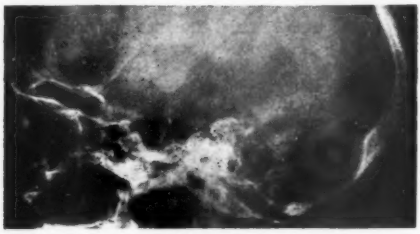


FIG. 1.

FIG. 1 is a radiograph of a young married woman of 21 years. Her periods commenced at 11 years and stopped at 16 years. She attended a women's hospital on two occasions and was duly reassured. Subsequently she developed headaches, associated with diplopia. She received a course of radiotherapy one year ago for suspected pituitary adenoma. To-day she is well and her periods have returned. Fig. 1 shows considerable expansion of the sella.

Early diagnosis of chromophobe adenomas in men is more difficult, but the following case is of interest.



FIG. 2.—November 1953.

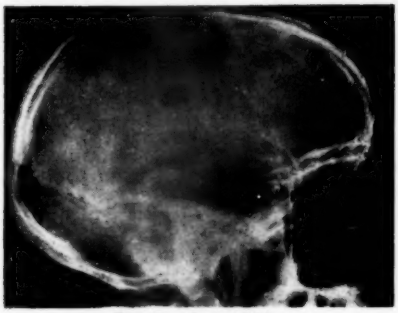


FIG. 3.—June 1954.



FIG. 4.—October 1957.

A young man of 25 was involved in a cycle accident in November 1953, and his skull was X-rayed for suspected fracture. No fracture was found, but the expanded sella suggested the possibility of pituitary tumour. As no significant change in the radiographic appearances was found some seven months later (*see* Figs. 2 and 3), medical observation was not continued. However, three and a half years later the patient developed frontal headache associated with impaired visual acuity and a bitemporal field defect. X-ray examination in October 1957 revealed considerable further erosion of the sella (Fig. 4). Craniotomy was then performed and the presence of a typical chromophobe adenoma confirmed.

It is most unusual to find a radiographically normal sella when a chromophobe adenoma is diagnosed. In the series under review the only instance occurred in a woman of 47 with an adenoma which had herniated through the diaphragma sellæ resulting in visual impairment.

*Principles of Radiotherapeutic Technique*

I shall discuss only the basic principles of method employed. One cannot overstress the importance of confining the zone of maximum dosage of radiation to the pituitary region and careful attention must be given to the question of beam direction. All the cases in the present series have been treated by conventional X-ray therapy using a beam of half value layer 3 mm.Cu. Five 4 cm. square fields are directed by means of a Perspex jig which rotates through the "pituitary axis". This axis is carefully checked by radiographic control using the treatment beam reduced to 90 kV.

[A series of slides was shown indicating the design of the treatment jig, and showing the patient "set up" in position for treatment. Dosage contours with five and eight field distributions were also illustrated.]

The dosage of radiation prescribed under the above conditions is 3,750 r maximum in four weeks. The prescribed dose was recently reduced from 4,000 r given in the same period.

With this method the skin at the treatment areas develops a mild erythema only and there is practically no constitutional disturbance. I consider that the method is more readily controlled than by any form of rotation therapy. Also, as the bone absorption factor in the relatively thin membrane bone of the skull is practically negligible there would not appear to be any particular advantage in employing supervoltage therapy in this situation.

*Response to Treatment*

*Chromophobe adenomas.*—Following the combined surgical and X-ray treatment, of the total of 165 patients comprising the series of chromophobe adenomas, 49 showed marked visual improvement in terms of full return of visual acuity and clearing of visual fields; 95 showed moderate visual improvement, and 21 showed no improvement.

The assessment was made up to a period of six months following the completion of the treatment, because the amelioration was sometimes delayed. In short, 87% of the treated cases showed some form of visual improvement.

The endocrine changes in chromophobe adenomas due to hypopituitarism are more difficult to assess. In many patients these changes were relatively modest and almost subclinical in type. In a smaller number the symptoms of obesity, somnolence, hypotension, pallor and extreme weakness were severe, leading to profound states of hypopituitarism.

Obviously, apart from surgery and radiotherapy the institution of endocrine replacement therapy by such agents as cortisone, thyroid and testosterone, is of the greatest importance. Fortunately, during recent years much more attention is being given to this side of the problem, as Dr. Leonard Simpson will indicate.

*Eosinophil tumours.*—The response to treatment is rather more difficult to assess, as a proportion of the cases are not associated with visual impairment. It would appear that the acromegalic process may be arrested by the irradiation, but it is not common for the characteristic facial features to change to any extent.

*Basophil tumours.*—All patients except one in this group showed some degree of improvement, and in three instances the improvement was striking.

[Slides were shown to illustrate the dramatic improvement occurring in two patients.]

*Craniopharyngiomas.*—The response to irradiation is decidedly encouraging in some cases. These tumours are by no means radio-insensitive as a class.

*Carcinoma.*—Although primary carcinoma of the pituitary is an uncommon disease, it is probably not so rare as is generally believed. There is increased evidence to show that the more cellular chromophobe adenoma can assume a malignant change. This has occurred in 3 of the patients in this group. 2 have died from intracranial metastases: one developed a large secondary growth in the right hemisphere, and the other separate masses over the meninges in the posterior fossa. 3 of the patients had original chromophobe adenomas which had become frankly malignant; the remainder were probably malignant from the outset.

### *Results Expressed in Survival Rates*

As these tumours are for the most part non-malignant and occur in a relatively young age group, one would expect the survival rates to be high. Tables II and III indicate the position in this series of cases:

TABLE II.—CHROMOPHOBE ADENOMAS (VERIFIED)

| *Progressive Survival Rates* | |
|---|---|
| 3 years | 83·6% |
| 5 years | 81·5% |
| 6 years | 79·0% |
| 7 years | 76·5% |
| 8 years | 72·4% |
| 10 years | 72·4% |
| 12 years | 69·3% |

TABLE III.—COMPARATIVE PATHOLOGICAL GROUP FIVE-YEAR SURVIVAL RATE

| | |
|---|---|
| Chromophobe adenomas | 81% |
| Eosinophil adenomas | 89% |
| Pituitary basophilism | 75% |
| Craniopharyngiomas | 75% |
| Carcinomas | 57% |
| Unverified adenomas | 60% |

### *Study of Deaths*

It is important to investigate the causes of death in the unsuccessful cases. There were 20 deaths in the series, and as far as can be ascertained the causes are enumerated:

(1) Intracranial extension of recurrent adenomas—6 patients.
(2) Extreme hypopituitarism—6 patients.
(3) Malignant transition in tumour—1 patient.
(4) Post-irradiation changes in brain—3 patients.
(5) Intercurrent disease—2 patients.
(6) Death occurring suddenly, of uncertain immediate cause—2 patients.

Successful treatment of patients depends essentially on team work and I would like to express my gratitude to all members of my staff at the radiotherapy centres at St. George's Hospital, London, and St. Luke's Hospital, Guildford, where the majority of these patients received treatment. Progressive improvements in the irradiation technique have been largely due to the energy and interest of Mr. C. Binks, senior physicist at the Guildford centre. My thanks are due to my colleagues, Mr. Harvey Jackson, Mr. Valentine Logue and Mr. Wylie McKissock for allowing me to include patients referred from the National Hospital, Queen Square, Maida Vale Hospital and Atkinson Morley's neurosurgical unit.

In conclusion it may be said that nowhere in the field of tumour treatment can radiotherapy combined with surgery give more promising results, and nowhere can the consequences be more serious unless the greatest care is given to the details of technique and clinical management.

### REFERENCE

HENDERSON, W. R. (1939) *Brit. J. Surg.*, **26**, 811.

Dr. **S. Leonard Simpson** (London):

*Endocrine Aspects*

In my brief observations, I shall consider two main types of pituitary tumour, chromophobe tumours with pituitary hypofunction, and eosinophil tumours with hyperfunction, acromegaly or gigantism, often combined with some aspects of pituitary hypofunction.

## Diagnosis

*Chromophobe tumours.*—These may remain unrecognized for ten or more years, and may present in limited form. Thus, one man of 51 had loss of libido and potency for sixteen years with progressive adiposity. Ultimate radiography of the skull for migraine showed extensive destruction of the sella turcica although changes in the fundi and visual fields were almost absent. Another man of 60 was treated for eight years with liver and iron for severe anæmia and much greater pallor, before visual impairment led to the correct diagnosis. Amenorrhœa, myxœdema, and migraine are other erroneous primary diagnoses which have been maintained for many years, in the absence of fundus examination and X-ray of the skull. Radiography is essential, as a tumour may be extensive with normal fundi. A simple lateral view of the skull is usually sufficient. The easiest way to avoid pitfalls of diagnosis, as above, is for the clinician always to bear in mind the possibility of insidious development of chromophobe adenoma.

I have not dealt with the more conventional symptoms of clinical pituitary hypofunction, e.g. anorexia, weakness, sensitivity to cold, &c., but would refer briefly to a number of laboratory tests based also on an associated secondary failure of adrenal and thyroid function, e.g. very low urinary values for 17-ketosteroid and 17-ketogenic steroids, low blood 11-oxysteroids, all three responding to ACTH stimulation except in some long-standing cases, insulin hypersensitivity or hypoglycæmic unresponsiveness, poor excretion of water load but corrected by cortisone, poor radioactive iodine uptake by involuted thyroid, &c.

*Acromegaly.*—Here also diagnosis may be delayed for many years, and clinical presentation may lead to a wrong or limited diagnosis. Two acromegalic women had large colloid goitres surgically removed fifteen and eight years before acromegaly was diagnosed, one being re-operated upon for recurrence. There is a definite association between such goitres and both gigantism and acromegaly, of practical and theoretical importance. Three women presented as idiopathic hirsutism. Cushing pointed out that the adrenals are often very large and nodular in acromegaly. Migraine and/or excessive perspiration may present for many years before true diagnosis. Impotence and/or azoospermia may be the only recognized features for some ten years, and one such patient referred from a sterility clinic became fertile and the father of two children after radiotherapy by Professor B. W. Windeyer. Sexual precocity or excessive sexual drive is a rare initial manifestation of acromegaly, but pituitary tumour is not a cause of a persistent syndrome of sexual precocity without acromegaly.

Rapid growth in childhood may be a precursor of acromegaly in later life. Cushing (1912) described very rapid growth in a male at 13, no acromegaly at 25, but death with acromegaly and eosinophil tumour at 32. I have seen a case of a girl with acromegaly, first obvious at 13, who had become suddenly tall at 5, 56 inches compared with average of 44 inches, very strong and a deep voice like the headmaster. Fundi known to be normal at 11. At 13, 6 ft. 6 in., 230 lb., fat abdomen, optic atrophy and bilateral hemianopsia. At 16, 6 ft. 10 in.; at 19, 7 ft. and 20 st. This is a sad example of mistaken masterly inactivity based upon the fallacious reasoning that the disease was quiescent because the fundi and fields remained the same from the age of 13. It is of interest that uncles and grand-uncles were over 6 ft., very strong and adipose, one a blacksmith weighing 40 st. Adiposity is not a common characteristic of acromegaly but it is a feature in some, and is probably associated with pancreatic islet cell hyperplasia, unless an extensive tumour invades the hypothalamus. Mild gigantism with slight acromegaly is familial, but two tall women with gross acromegaly had many gigantic males in the family, 6 ft. 4 in. or more in height, but without gross acromegaly.

## Treatment

The discovery and availability of cortisone, hydrocortisone and prednisone have made substitution therapy for pituitary hypofunction more comprehensive, and, in particular, have made surgery of the pituitary gland a much safer procedure, endocrinologically speaking, in the same way as they have made bilateral adrenalectomy a practical and safe procedure. It seems prudent to give one of these substances before operation and to continue after operation until the need for and amount of a maintenance dose is decided. In so far as aldosterone secretion persists after hypophysectomy (Maclean *et al.*, 1957), except perhaps in some long-standing cases, prednisone seems to be slightly preferable to

cortisone in that its sodium-retaining action is negligible. Cortisone has the advantage over prednisone for the operative period, of being available for intramuscular injection as well as by the oral route, and hydrocortisone in alcoholic solution or in the form of the water-soluble succinate can be given intravenously, the latter directly in small volume, 100 mg. in 2 ml. Although pituitary operations were frequently successful prior to the era of cortisone, some patients collapsed and died after relatively minor surgical interference, and cortisone diminishes this hypersensitive reaction of pituitary-insufficient cases to minor and major surgery.

For substitution therapy, in hypopituitarism both before and after operation, testosterone and thyroid are important adjuncts to prednisone. Unlike its negligible effect in Addison's disease, testosterone by itself has a valuable and often dramatic effect in pituitary hypofunction as was illustrated by two cases of surgically treated pituitary chromophobe tumour reported to the Society (Simpson and Taylor, 1947; Simpson and Wright, 1947), as well as in a series of cases of Simmonds's disease (Simpson, 1948). One of these tumour patients, now 79, on methyltestosterone, is so well and so youthful as to suggest hypophysectomy as a routine procedure for rejuvenation and longevity. Neither cortisone nor testosterone should be given in doses above the minimum required to obtain clinical results, as large doses are disturbing, especially in the case of prednisone or cortisone. Prednisone is especially valuable in those patients who tend to hypoglycæmia, anæmia (Summers, 1952), or water intoxication. Adrenocorticotrophic hormone (ACTH) is a logical alternative to prednisone and testosterone combined, but has the disadvantages of requiring daily injections, producing side reactions in some, being ineffective after a while because of antibodies, or failing to secure an adrenal response in long-standing cases. Pituitary growth hormone is not yet available and, apart from the disadvantages of injections, is not essential except perhaps for skeletal growth, testosterone being protein anabolic.

Œstrogens in large doses are clinically effective in some patients with acromegaly, and can diminish pituitary diabetes and improve visual fields (McCullagh *et al.*, 1955), but fundamentally I consider them to be of limited value. In gigantism in adolescent girls, œstrogens accelerate union of the epiphyses.

Both for purposes of diagnosis and for determining treatment, it is valuable to have laboratory aids to clinical judgment as to the activity of an acromegalic process, or, in other words, the extent of hypersecretion of growth hormone. Raised inorganic phosphorus (Li *et al.*, 1949) and increased urinary creatine or creatinine excretion are simple but somewhat unreliable indications. The measurement of plasma insulin by uptake of glucose by the rat's isolated diaphragm (Randall, 1954; Randall and Young, 1956) is, in my clinical experience, of considerable value and reliability when carried out under tested conditions and compared with a pool of normal plasma. This test is in keeping with the important post-mortem findings of Cushing and Davidoff (1927) of the frequency of pancreatic islet cell hyperplasia and hypertrophy in acromegaly, and is supported by animal experiments with growth hormone.

Finally, the need for surgery, or radiotherapy, in acromegaly should not be determined solely by encroachment on the fundi and visual fields. Clinical and biological evidence of progressive pituitary hyperfunction is at least of equal importance now that substitution therapy for any subsequent pituitary hypofunction is on a sound basis. It is well known in endocrinology that the degree of hyperfunction is not related to the size of an endocrine neoplasm.

## REFERENCES


CUSHING, H. (1912) The Pituitary Body and Its Disorders. Philadelphia.

——, and DAVIDOFF, L. M. (1927) *Monogr. Rockefeller Inst. med. Res.*, No. 22.

LI, C. H., GESCHWIND, I., and EVANS, H. M. (1949) *Endocrinology*, **44**, 67.

MCCULLAGH, E. P., BECK, J. C., and SCHAFFENBURG, C. A. (1955) *Diabetes*, **4**, 13.

MACLEAN, J. P., LIPSETT, M. B., LI, M. C., WEST, C. D., and PEARSON, O. H. (1957) *J. clin. Endocrin.*, **17**, 346.

RANDALL, P. J. (1954) *Lancet*, i, 441.

——, and YOUNG, F. G. (1956) *J. Endocrin.*, **13**, 335.

SIMPSON, S. L. (1948) *Proc. R. Soc. Med.*, **41**, 192.

——, and TAYLOR, J. (1947) *Proc. R. Soc. Med.*, **40**, 151.

——, and WRIGHT, A. D. (1947) *Proc. R. Soc. Med.*, **40**, 151.

SUMMERS, V. K. (1952) *Brit. med. J.*, i, 78.

# Section of Ophthalmology

President—J. R. WHEELER, F.R.C.S.Ed.

[*March* 13, 1958]

## The Clinical Features of Viral Keratitis and a Concept of Their Pathogenesis

By BARRIE R. JONES, F.R.C.S.

*Institute of Ophthalmology, University of London*

THE viruses concerned in causing keratitis are well known. In our classification it is apparent that herpes means herpes simplex and zoster means herpes zoster (Table I).

TABLE I.—VIRUSES CAUSING KERATITIS

A. Regular corneal viruses:
- Herpes
- Zoster
- Adenoviruses
- Trachoma
- Inclusion conjunctivitis

B. Occasional corneal viruses:
- Measles
- Vaccinia
- Mumps
- Behcet's syndrome
- Reiter's syndrome

C. Viruses causing skin lesions on lid margins with secondary keratitis:
- Molluscum contagiosum
- Warts

Viral diseases of the cornea result chiefly in four types of keratitis—punctate, dendritic, disciform and other types of parenchymatous keratitis. Some twenty-five years ago Doggart (1933) urged that since the name "superficial punctate keratitis" conveyed different meanings to different people its unqualified use led to confusion and was to be avoided. The intervening years have doubled the confusion, and now that ætiological diagnoses are possible it is becoming apparent that more than one agent may give rise to a clinical picture resembling that to which Fuchs originally applied the name. It is hopeless to restrict the meaning of the term which has become thus diversified; we had better acknowledge that it means only that our patient has small spotty lesions on the front of his cornea and admit that the precise morphology, cause, prognosis and response to treatment are in no way specified by this name. I recognize the following types of spotty corneal lesions (Table II), each one of which would be described as "superficial punctate keratitis" by some author or another (Jones *et al.*, 1957).

TABLE II.—CLINICAL TYPES OF "SUPERFICIAL PUNCTATE KERATITIS"

1. Punctate epithelial erosions
2. Punctate epithelial keratitis: Fine
   Coarse
   Areolar
   Stellate
3. Deep punctate epithelial keratitis (sometimes with opacification in Bowman's membrane)
4. Combined epithelial and subepithelial punctate keratitis
5. Punctate subepithelial keratitis
6. Interstitial punctate keratitis

Punctate epithelial erosions are minute lesions which are almost invisible with the microscope unless stained by fluorescein and *all* the free dye washed out. Each one is then seen as a brilliantly stained minute depression. Fluorescein stains breaches in the epithelium or immature epithelial cells revealed by premature desquamation. Hence,

these erosions often accompany other lesions. They are non-specific for they may occur in almost any of the viral diseases of the cornea or with warts or molluscum contagiosum of the lids. The most frequent cause is a staphylococcal blepharitis. They also result from industrial irritants such as hydrogen sulphide, from exposure keratitis and in keratoconjunctivitis sicca. They may be found in corneal œdema regardless of the cause, whilst sometimes their ætiology is obscure.

In punctate epithelial keratitis the spots are opaque, slightly raised and visible with the slit lamp. They stain poorly with fluorescein but take up bengal rose. It seems that a drop of 1% dye, which need not be washed out, stains diseased or hypermature epithelial cells—whether the alteration is due to virus invasion, desiccation or simply delayed desquamation resulting from padding an eye. It will also stain the mucus and debris which collect on an ulcerated area of cornea, but only viral invasion of the epithelium produces the ordered collection of white dots which stain with bengal rose.

Punctate epithelial keratitis may be fine, coarse, areolar or stellate. With the last two varieties the lesions look punctate to the naked eye or loupe, but the microscope reveals their true shape.

In deep punctate epithelial keratitis the lesions are deep in the epithelium and sometimes associated with opacities in Bowman's membrane. Their staining is variable. They are often associated with rosacea, respond to cortisone and do not appear to be of viral origin.

Combined epithelial and subepithelial punctate keratitis leading on to punctate subepithelial keratitis following about two weeks of follicular conjunctivitis is the sequence of events so well known in epidemic keratoconjunctivitis. It should be noted that since the epithelial component is small, stains poorly with fluorescein and is transient it is easily overlooked. The clear gap, corresponding with Bowman's membrane, separating the subepithelial reaction from the epithelial disease is a constant feature in viral keratitis.

Combined lesions going on to subepithelial keratitis of varying severity result not only from adenovirus infection by types 8, 7 and 3 viruses, but also from herpes, zoster, vaccinia and other viruses. Because of their severity and duration, cases of this type due to inclusion conjunctivitis are perhaps the most worrying and since specific treatment is available it is important to recognise them. The fleshy hyperplastic follicular conjunctivitis with slightly yellowish follicles on the plica and caruncle lasting for more than three weeks should make us suspect the disease and an examination of scrapings will confirm the diagnosis. It is taught that the cornea is not affected, and in fact this is supposed to be one of the chief points distinguishing it from trachoma. I cannot emphasize too strongly that this is entirely wrong so far as the disease in London is concerned. It frequently produces a general roughening of the epithelium with foci of epithelial disease. If these persist a rather dirty looking subepithelial punctate reaction ensues and may go on for many months. I have succeeded in demonstrating the cytoplasmic inclusions characteristic of the disease within a corneal epithelial cell from a lesion. The reservoir of infection is in the female cervix and nearly every case can be traced there via either urethra or fingers. In some cases I have noted a rather severe chronic rhinopharyngitis in association with the ocular disease. All these features respond to adequate treatment with oral sulphonamide and local Achromycin, although it is desirable to continue treatment for a month to prevent relapses.

Interstitial punctate keratitis describes the deeper punctate lesions which may rarely occur in herpes and other conditions.

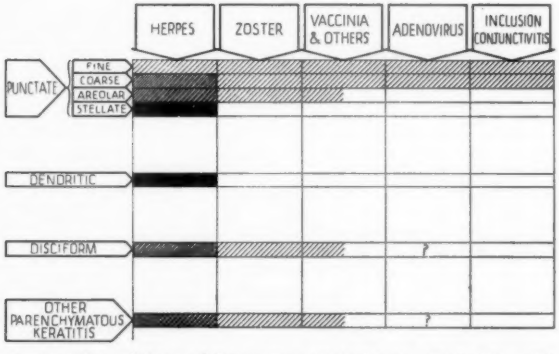



FIG. 1.—The ætiology of the various clinical types of viral keratitis.

*Shape of the lesions.*—Fig. 1 indicates that coarse punctate lesions suggest adenovirus, herpes, zoster or inclusion conjunctivitis, areolar lesions strongly suggest herpes, whilst stellate or dendritic ones occur only in herpes and this disease accounts for the bulk of disciform and other parenchymatous keratitis. It will be realized that in many cases it is the march of events which points to the diagnosis.

Before considering the ravages which herpes simplex may produce on the cornea, we should remember the patient with diphtheria whom we treated with intravenous injections of antitoxin. He recovered from his infection but in the second week his temperature rose, he felt ill and was found to have enlarged lymph nodes. He developed an urticarial rash which soon spread nearly all over him. His throat was sore and his joints were swollen. He was suffering from serum sickness. When we injected the foreign proteins in the horse serum into his blood some became fixed on cells in his blood vessel walls and other tissues (Wright, 1953). No harm resulted until during the second week he produced antibodies to these foreign antigens. The union between antibody and antigen fixed on cell membranes gave rise to cell damage and the clinical features which we recall.

Clinical and pathological observations agree that the viruses under consideration grow in the epithelial cells of the cornea and they are not capable of extracellular multiplication. Hitherto it has been tacitly or explicitly stated that parenchymatous viral keratitis is due to deeper invasion by the virus. I believe that this is an unjustified assumption, for the stroma is a remarkably unpromising looking tissue in which to grow these epitheliotropic agents. Instead I propose my concept of the corneal stroma as an immunological blotter (Fig. 2).

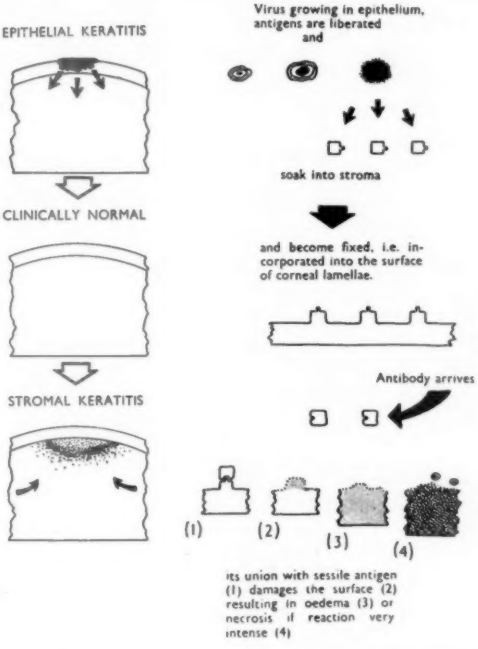



FIG. 2.—The corneal stroma as an immunological blotter in primary viral keratitis.

I postulate that the virus grows in the epithelial cells alone and in killing them liberates antigens which soak into the underlying stroma to become fixed in the surface of fibre and cell membranes. No damage results until antibodies arrive from the blood stream or are produced locally. Antibody reacting with herpetic antigen sessile on the surface of corneal lamellæ would cause altered permeability and stromal œdema resulting in opacity. If the reaction were very intense necrosis would result.

This is the only hypothesis which explains certain remarkable but hitherto unrecorded features of primary corneal herpes. In an initial infection there is no stromal reaction under central epithelial lesions during the first two to three weeks (Fig. 3). The epithelial disease may resolve or be removed by cotton-wool and may heal entirely and yet in the second or third week subepithelial reactions will occur in spite of overlying normal epithelium. If,

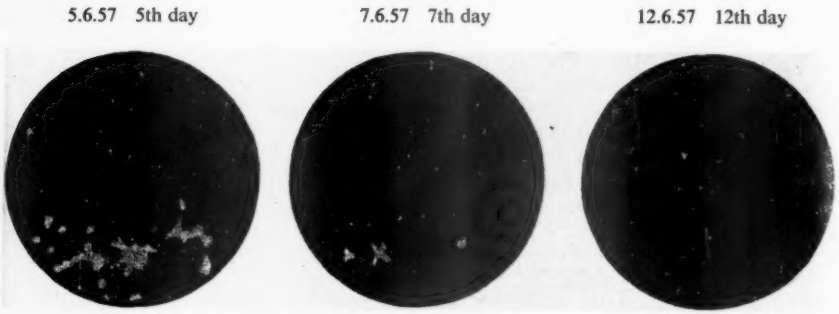



FIG. 3A.

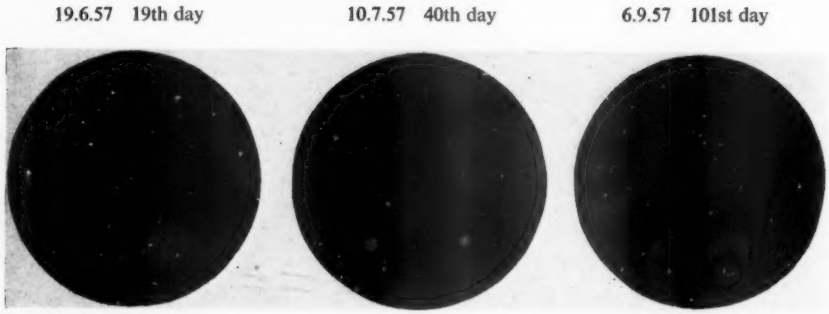



FIG. 3B.

FIG. 3.—The clinical course of primary herpes simplex keratitis. Note that the cornea was clear on day 12 after epithelial keratitis had resolved. Nevertheless, stromal reaction occurred on day 19 under the previous sites of the most persistent epithelial lesions.

however, the lesion is marginal and associated with a limbal follicle the subepithelial reaction may commence much earlier. In this case antibody is probably being produced locally.

The more extensive the epithelial lesions and the longer they are allowed to persist the more likely is the stromal reaction to go straight into a disciform keratitis with K.P. on the back of the affected area. It is likely that the flare, cells, K.P. and even hypopyon represent the uveal response to the antigen-sodden cornea; similarly, the lymphocytic and plasma cell infiltrate which may occur in the iris probably indicates local antibody production rather

than a uveal invasion by virus. Experimental work (Oakley *et al.*, 1955) suggests that it may even be possible for antigen to become fixed in the iris and so give rise to a damaging reaction when antibody arrives.

If a disciform reaction is eccentric or so extensive that the periphery is involved there is usually a rise in tension. This occurs in the absence of heavy flare or thick exudate, without iris bombé and with a manifestly wide angle, which may, however, show K.P. on the trabecular zone. I postulate that in these cases so much antigen has soaked in that it has become fixed in the trabecular tissues (Fig. 4). The ensuing union with antibody has given



FIG. 4.—A, Antigen soaking into the trabecular meshwork and becoming fixed. B, The arrival of antibody gives a damaging reaction with secondary glaucoma.

œdema and led to reduced outflow with secondary glaucoma. This is usually reversible. Those eyes which I have seen which developed grossly defective perception and have been removed to relieve pain have all either perforated or suffered some anterior chamber collapsing procedure to relieve tension. Even a paracentesis allows the sticky iris to come into contact with the antigen-sodden cornea and irreversible synechiæ result. The eye is blinded and lost, not from intra-ocular virus invasion but from a disastrous secondary glaucoma. If the anterior chamber is lost an extensive basal iridectomy might offer the best chances.

Whereas in primary or initial corneal herpes there is no stromal reaction for about two weeks, in the recurrent episodes it ensues within a few days and the epithelial lesion is more prone to ulcerate. If the patient has not had a herpetic episode for many years the reaction may be delayed several days. I postulate that once again the epithelial lesion supplies antigen to the underlying stroma and that there must be an immediate local excess of antigen so that it neutralizes any antibody present and becomes fixed on the tissues. The accelerated arrival of antibody then produces a reaction as before. This must be very similar to what happens in the skin when one injects herpetic antigen to demonstrate a delayed skin sensitivity or carries out a Frei test.

If an epithelial recurrence occurs over an area which has recently been the seat of stromal disease the stroma appears to be prone to necrose and excite a polymorph response. It is as though the vital surfaces can only tolerate a certain amount of immunological neutralization. It is also likely that the damaged cornea is more permeable to antigen than is the normal. This necrotizing reaction is more liable to occur with cortisone treatment but may occur without it.

Like Thygeson *et al.* (1956) I have avoided the term metaherpetic keratitis, which has been applied to indolent corneal herpes, often with ulceration and marked œdema. It was supposed by Braley (1952) to occur in patients who had become hyperimmune to herpes. I would suggest that it is the picture of an antigen-sodden cornea being neutralized but since the term takes no cognizance of whether active viral epithelial disease is present or not it is no guide to treatment and I have no use for it.

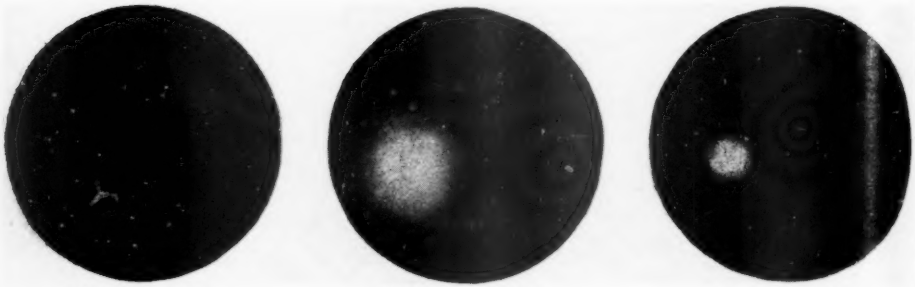
*Treatment.*—My concept of the disease gives every possible support for the time-honoured treatment by removal of the epithelial lesion and unless carbolic or some other disinfectant is applied fresh spots may break out on the edges of the abraded area. Furthermore, we must maintain the most careful watch throughout the illness for recurrence of epithelial viral disease, especially if cortisone is used, and deal with it immediately. Atropine is required but antibiotics can do no more than prevent secondary infection.

The fierce arguments which centre around the place of cortisone in treating herpes are well known. Whereas the body of American opinion emphatically condemns it, in London many believe that its use is valuable and safe provided there is no staining by fluorescein. This controversy can be resolved by considering the effect on the epithelial and stromal components separately.

8.3.57
16th day

15.3.57
23rd day
Cortisone treatment →

3.5.57
66th day
Cortisone withdrawn →



Epithelial keratitis, early stromal reaction

Epithelium healed, severe stromal reaction

Stromal reaction minimized



FIG. 5A.

21.5.57
101st day
Cortisone treatment →

28.5.57
108th day
Cortisone continued →

25.6.57
143rd day
Cortisone withdrawn →



Reappearance of stromal reaction

Stromal reaction minimized

Further resolution



FIG. 5B.

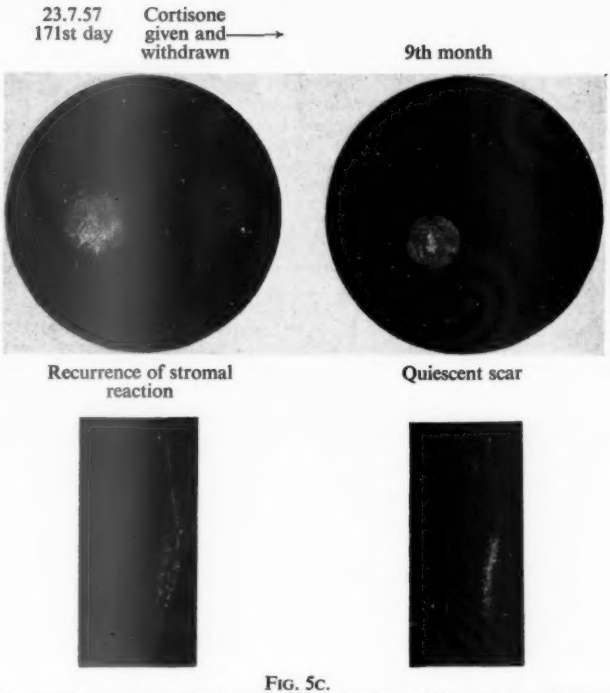



FIG. 5c.

FIG. 5.—The reversible clinical effect of topical cortisone administration on stromal keratitis in herpes simplex.

The epithelial lesion is not healed by cortisone and under its influence there may be a greater tendency to extension and recurrence. The danger lies in the fact that with the eye rendered white and comfortable the clinician may fail to deal with the epithelial lesion. The stroma becomes more and more antigen sodden until it is doomed to a necrotizing reaction, perforation ensues and the eye is lost. Therefore if we use the drug we must intensify our watch on the epithelium.

If the stromal disease is purely an immunological reaction we would expect cortisone to control it. Fig. 5 shows how it minimizes the œdema, dissolves the smaller foci and diminishes the larger ones. Its premature withdrawal allows them to return or recrudesce but eventually it can be withdrawn without deterioration. In the same way steroids control the trabecular and uveal reaction; although Diamox may also be needed we should never sacrifice the anterior chamber with the knife.

In certain cases with marked œdema the epithelium simply fails to heal after the viral plaque has been removed or an epithelial bulla has ruptured. The breach stains with fluorescein but bengal rose reveals no active viral disease. Further cauterization is futile, one hesitates to use cortisone but tarsorrhaphy is of the greatest value.

Although we do not know exactly how cortisone acts it may work through vasoconstriction and reduced capillary permeability cutting down the supply of antibody to the cornea. This may explain how superficial irradiation produces a rather similar result with less tendency to epithelial recurrence than the use of cortisone entails.

For a severe keratitis which is likely to go on for months I believe that after controlling any trabecular and uveal reaction, the best treatment lies in the removal of the bulk of antigen-sodden tissue by a lamellar graft. A perforating graft would be better but would entail the iris touching the cornea and this could not be countenanced even for a moment. If the anterior chamber has already been lost the best prospect of avoiding intractable glaucoma lies in doing a broad basal iridectomy as soon as possible.

The other therapeutic possibility which Dr. F. O. MacCallum and I hope to explore lies in the application of human gamma-globulin of known antiherpetic titre in the form of drops. Experience with vaccinial keratitis suggests that it may be of value in preventing antigen soaking into the cornea by achieving a more superficial neutralization.

Some success in preventing recurrences of corneal herpes may come from elucidating the trigger factor in each case and attempting to eliminate it by the control of pyrexial episodes with aspirin and other antipyretics, by sedatives or avoiding excessive sun-light, heat and cold, or the use of protective glasses. Superficial irradiation may have a place but corneal grafting nearly always prevents further recurrences.

Primary corneal herpes may be prevented by teaching that recurrent labial or other herpes is infectious to a susceptible person. When an initial herpetic blepharoconjunctivitis presents, the cornea may be protected by careful toilet of lid margin vesicles and the application of alcohol or other disinfectants to these lesions.

*Acknowledgments.*—I am indebted to Drs. F. O. MacCallum, B. E. Andrews and L. A. Hatch of Colindale, and Dr. W. G. Henderson of the Institute of Ophthalmology, for all their work in establishing ætiologies.

## REFERENCES

BRALEY, A. E. (1952) *Amer. J. Ophthal.*, **35,** 1737.
DOGGART, J. H. (1933) *Brit. J. Ophthal.*, **17,** 65.
JONES, B. R., ANDREWS, B. E., HENDERSON, W. G., and SCHOFIELD, P. B. (1957) *Trans. ophthal. Soc. U.K.*, **77,** 291.
OAKLEY, C. L., BATTY, I., and WARRACK, H. (1955) *J. Path. Bact.*, **70,** 349.
THYGESON, P., KIMURA, S. J., and HOGAN, M. J. (1956) *Arch. Ophthal., Chicago*, **56,** 375.
WRIGHT, G. P. (1953) In: Recent Advances in Pathology. Edited by G. Hadfield. 6th ed. London; p. 38.

### DISCUSSION

In reply to a question, **Mr. Jones** said that he had avoided mentioning the disease named "superficial punctate keratitis" by Thygeson (1950) because the name was not generally adopted for this condition in this country and its use adds to our confusion. In Europe, where "superficial punctate keratitis" means, to many, the epidemic subepithelial disease following conjunctivitis, it appears strange that Thygeson should apply it to a new clinical entity. But in America the subepithelial disease is clearly designated by the excellent name of epidemic keratoconjunctivitis, so that to Thygeson "superficial punctate keratitis" must have appeared as a name in search of a disease!

Braley and Alexander (1953) claimed to have isolated a virus from the disease but the work has not been confirmed, and since the original agent is not available it is not possible to make an ætiological diagnosis. For clarity it is probably best to refer to the condition as "Thygeson's punctate epithelial keratitis".

## REFERENCES

BRALEY, A. E., and ALEXANDER, R. C. (1953) *Arch. Ophthal., Chicago*, **50,** 147.
THYGESON, P. (1950) *J. Amer. med. Ass.*, **144,** 1544.

[*June* 12, 1958]

# DISCUSSION ON ERYSIPHAKE EXTRACTION OF CATARACT

**Mr. E. C. Zorab** (Southampton):

*Extraction of the Lens with the Erysiphake*

In speaking about the extraction of the lens with the erysiphake, I shall confine my remarks to the manœuvre of removing the whole of the lens.

The erysiphake was in use in Barcelona in 1916 and in New Zealand in 1920. Through the years many different instruments have been produced and many different forms of suction used. Until recently none of them has been entirely satisfactory. It was my good fortune to see Mr. Cogan operating at Tunbridge Wells at a time when I was concerned about the number of "failed intracapsular" cases I had with the technique I was then using. This was tumbling with the Arruga forceps and counter pressure below.

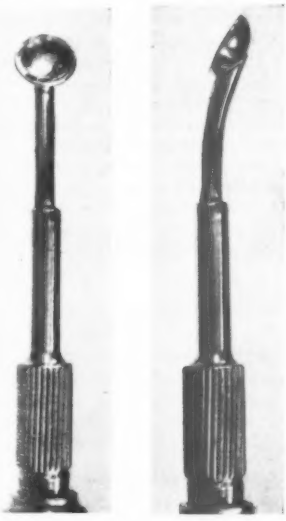
I was also concerned about the number of aphakic detachments in my cases—amounting to about 1½%—which, rightly or wrongly, I ascribed to my technique. I was even more ready for a change of technique when, in company with Mr. Cogan, I had visited the Barraquer Clinic and watched a large number of erysiphake extractions as well as many other beautiful operations. Shortly after this, I heard Dr. Derrick Vail give his Doyne Memorial Lecture on the zonule. And it seemed to me that the surgical technique I had been watching was the logical outcome of Dr. Vail's researches—although preceding them by many years.

Whatever may be the method of premedicating the patient, I believe that the tone of the extra-ocular muscles is the most important thing to dispense with, whether by general or local anæsthetic or by curarization. If this is done satisfactorily there need be no loss of vitreous. I believe that massage of the globe is useless.

Fig. 1 A and B shows the business end of the erysiphake which I use and which is made of platinum. Fig. 2 is a schematic drawing of the instrument. The overall diameter of the cup is 5·5 mm. The rim is 0·75 mm. wide, so that the inner diameter is 4 mm. This means that traction on the capsule is distributed over an area 12 sq. mm. and 12 mm. in circumference. It will be realized that this is two or three times as great as can be obtained with forceps.

Next, the clearance between the edge of the cup and the stem should be noticed. This enables the cup to be insinuated beneath the pupil margin—thus avoiding catching iris in the cup. The position of the hole is important; if it is not kept away at the edge, the capsule is easily sucked into the hole and either ruptures or prevents sufficient suction being obtained. The acute-angled ridge gives a firmer grip on the capsule. The dome is designed to be of such size that an average cataract will mould into it with tension insufficient to rupture the capsule. The curve in the stem is for ease of manipulation and the handle is merely a matter of personal choice.

One final point—the instrument has a screw cap which prevents damage to the cup, as it is vitally important that there should be no rough edge to injure the capsule. Suction is provided by an electric suction pump, which is controlled by a foot switch and has a screw valve which can vary the degree of suction as indicated by a gauge. The degree of suction is important. The ordinary senile cataract needs about 450 mm.Hg. The cataract with a strong capsule and a large hard nucleus may need over 500, but the intumescent cataract with a weak capsule will only take about 300 or 350. It has often been suggested that there might be a control on the handle of the instrument instead of the foot switch. Personally, I prefer an instrument to serve one purpose and I dislike gadgets on the handle. I think it can then be manipulated more carefully and delicately.



A B

FIG. 1.—A, Barraquer erysiphake. B, Lateral view of Barraquer erysiphake.



FIG. 2.—Schematic drawing of erysiphake.

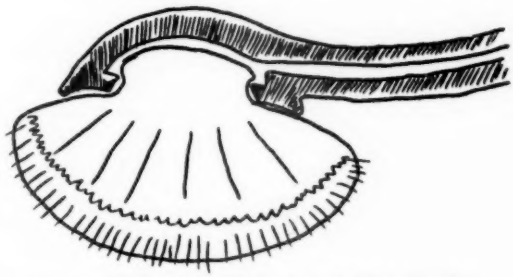


FIG. 3.—Composite drawing of erysiphake grasping a cataract. Note the traction folds in the capsule, the zonular attachment drawn upwards, and the zonular fibres in view at the edge of the lens. The capsule and cortex are moulded into the dome of the erysiphake leaving a small air space.

As an alternative to the electric pump, I have often used the British Oxygen Company's injection-type sucker which works from an oxygen cylinder on the same principle as a Spengel's pump. It is useful to have an alternative, since electric devices sometimes fail to work, and this type of sucker is found in many operating theatres as part of the anæsthetic equipment. Having opened the eye (which I personally do with a Graefe knife) and having made a peripheral iridectomy and put in one corneo-scleral suture, I then clean out the anterior chamber with irrigator or brush and make sure there is no blood clot which might hamper suction. I then insert the erysiphake at 10 o'clock with the assistant holding open the wound. I place it on the anterior surface of the lens without any backward pressure, making sure that the cup is in contact with the lens all round and is not tilted. With a wide pupil this is easy. With a smaller pupil the cup can be insinuated through the pupil

and then moved in a rotary fashion as if polishing, in order to let the pupil margin ride over the edge and to feel that the cup is flat. The suction is then switched on with the foot switch and three or four seconds are allowed to elapse while the suction is building up. During this time, three things happen:

Firstly, the capsule is put under tension as it is drawn up into the cup.

Secondly, the lens becomes moulded into a more spherical shape by the tension which reduces its diameter.

Thirdly, the drawing up of the anterior capsule brings the anterior zonule attachment towards the centre, thus putting it also under tension (Fig. 3). When the desired degree of suction is reached, recorded by the gauge, the erysiphake is lifted directly forwards a little at the same time as counter-pressure is applied at 6 o'clock. This starts the stripping off of the zonule attachment which is continued by rotating the erysiphake, tumbling the lens at the same time that the counter-pressure instrument—perhaps a squint hook—is slid up the surface of the cornea, tucking it in behind the lens. The division of force between these two manœuvres is a matter for the individual. I rather disagree here with Vail, who recommends 5% pull and 95% push. I would rather say 80% pull and 20% push, but, of course, these forces vary from the start to the finish of the manœuvre and also from case to case.

The actual manœuvre is quite quick, taking only perhaps 5 to 10 seconds. It occasionally happens that the capsule ruptures. When it does so, it is the posterior and not the anterior surface which ruptures, and this is presumably due to excessive tension on the capsule by suction. It will also occasionally happen that the lens will draw out with it a thin cone of vitreous when the posterior capsule has become adherent to the vitreous face, particularly in young people. This can usually be separated or cut by the assistant without loss of vitreous. It is not essential that the lens be tumbled out. It can be rotated out, pulled directly upwards or even brought out sideways, but tumbling seems the easiest and least traumatic way, unless the lens is so large, flat and rigid that it is likely to traumatize the tissues in somersaulting—in which case it is probably best drawn upwards over the upper edge of the pupil margin.

I have been much happier using this technique than with any previous one. I have been impressed with the lack of operative trauma and, therefore, with the quietness of the eyes afterwards. Out of some 50 cases, I have broken three capsules. In one I let the suction build up to 650 by mistake. Another was a complicated cataract where I was particularly anxious not to break it, and a third was in removing a cataract through a 6 mm. perforating graft. In this latter case, the erysiphake was at fault as it was blocked. However, even when the capsule breaks, it usually comes out complete leaving the lens behind, which can then be removed. I have done several cases in the 30s and 40s in whom I am quite sure the capsule would have ruptured with forceps.

A short film was then shown of how the operation should be performed. It was made in the Barraquer Clinic and the operator was Dr. Joaquin Barraquer. This film is a copy and belongs to the Tunbridge Wells Group Hospital Management Committee—by whose kind permission it was shown.

## REFERENCES

COGAN, J. E. H. (1957) *Trans. ophthal. Soc. U.K.*, **77**, 585.
VAIL, D. (1957) *Trans. ophthal. Soc. U.K.*, **77**, 441.

**The President** asked how the pressure was kept even, after the erysiphake was applied.

**Mr. Zorab** replied that provided the machine was working properly, if the pressure was set before the operation at what was thought would be needed, say 450, once it had built up to 450, and the lens was gripped, the pressure would stay at 450 so long as the foot was kept on the switch or the erysiphake did not slip off the lens.

**Mr. Frank Law** suggested that the manœuvre must require a 180-degree section of the cornea.

**Mr. Zorab** replied it would be not larger, and possibly rather smaller than that for use with forceps. The lens is more spherical when it is coming out with an erysiphake than when coming out with forceps.

**Mr. C. Dee Shapland** asked what type of suction apparatus Mr. Zorab was using. He, himself, had had imported to Moorfields the apparatus now being used at the Barraquer Clinic.

**Mr. Zorab** replied that the electric suction apparatus he used mainly was a home-made one which worked extremely well. Its components were obtained from a Government surplus store, at a cost of £10. It was constructed from the original design of Dr. M. Garber. The Barraquer instrument, being designed for the purpose, was, of course, somewhat superior, but much more expensive.

**Mr. E. F. King** said that he had seen Mr. Zorab carry out this operation on a number of cases. He himself had used the erysiphake a few times and, although the operation itself had gone smoothly, he had been worried by an undue amount of post-operative striate keratitis.

Mr. **Zorab** said he would agree that this was so in the first day or two after operation. It was probably due to the metal dome of the erysiphake rubbing the surface of the cornea after the lens was tumbled, and to wrinkling of the cornea. It disappeared in a very few days.

Mr. **Nigel Cridland** asked Mr. Zorab what were the criteria, looking at the eye pre-operatively or during the operation, which decided him what pressure to set on the machine. Could he reduce the suction immediately if necessary?

Mr. **Zorab** said he had not yet found it necessary to reduce the pressure very suddenly, as no emergency had occurred when he wanted to stop it quickly. As soon as the foot was taken from the switch the motor stopped and the needle went back gradually. When he had wanted to release the suction he had found that acted quickly enough. He thought a trigger on the handle might be released inadvertently, causing a loss of suction when it was needed. As regards the first part of the question—he had touched broadly on this subject in his paper, and his experience was insufficient to lay down more detailed criteria.

**Mr. J. E. H. Cogan** (Tunbridge Wells):

*Enzymatic Zonulolysis*

Dr. Joaquin Barraquer, of the Barraquer Institute, Barcelona, has discovered a lytic action of a proteolytic enzyme on the zonule. It deals with alpha-chymotrypsin, an endopeptidase gifted with fibrinolytic and proteolytic action.

This substance, injected in the anterior chamber of the human eye, seems to have a selective lytic action on the zonule, while respecting the remaining endocular structures. This action is made evident by the subluxation of the lens a few minutes after the zonulocamerular irrigation with this enzyme. When the lens has been extracted, the author has noted by means of biomicroscopy during the post-operative period the absence of corneal, irideal, hyaloid, retinal, &c., alterations which could be attributed to the ferment or enzyme.

The author believes that enzymatic zonulolysis opens a new surgical field of the crystalline lens seeing that:

(1) The intracapsular extraction is possible at any age, which

(2) Renders extracapsular extractions unnecessary and in consequence its inherent complications are not presented, such as: capsular retraction; secondary cataract; iridocapsular synechiæ.

(3) The following accidents that sometimes occur during and after intracapsular extractions are eliminated: tearing of the capsule; iridocyclitic operational injuries; loss of vitreous humour due to push-and-pull manœuvres employed for the extraction; retinal detachment due to excessive tractive efforts as mentioned above.

(4) It advantageously replaces the mechanical zonulotomy technique employed up to the present.

ALPHA-CHYMOTRYPSIN

Alpha-chymotrypsin is a proteolytic enzyme obtained from its inactive precursor alpha-chymotrypsinogen which is extracted from bovine pancreas.

Alpha-chymotrypsin splits different linkages in peptide chains than does trypsin and, unlike trypsin, it does not clot blood. The enzyme is most active between pH 8·0 and pH 9·0 and its activity is greatly enhanced by the presence of calcium ions.

*Assay.*—Anson's hæmoglobin method of assay is used. The activity is expressed in terms of hæmoglobin units and that of crystalline material is 6·0 units per gram of protein (Northrop *et al.*, 1948).

Alpha-chymotrypsin is prepared from 3× crystallized alpha-chymotrypsinogen and is itself 3× crystallized, the final crystallization being from 20% ethanol. It is salt-free and trypsin-free and its activity is of the order of 6·0 hæmoglobin units per gram of material.

CLINICAL APPLICATION

5 mg. of 570 Armour units (freeze dried) alpha-chymotrypsin is dissolved in 25 ml. Ringer's solution to produce a 1/5,000 solution. This solution loses 20% of its stability at room temperature after four hours, but if kept at 5° C. (refrigeration) maintains 60% stability for a month. The 1/5,000 solution will no doubt be marketed in 1 ml. quantities so that this quantity will be sufficient for four cataract extractions.

*Operative technique.*—(1) Corneoscleral conjunctival incision.

(2) Peripheral iridectomy.

(3) A sterile 1 ml. syringe containing 1/5,000 solution of alpha-chymotrypsin and lacrimal needle is passed through iridectomy: 0·25 ml. of solution is then ejected to flood the anterior surface of lens and upper segment of zonule. Zonulolysis takes three minutes.

(4) One subconjunctival corneal suture is passed using methylene blue stained virgin silk carried by a 4 mm. Grieshaber No. 83 needle and special needle holder. The suture is hooked aside to allow of wide opening of wound.

(5) After exactly three minutes—no less—the anterior chamber and subiritic angles are irrigated with Ringer's solution to remove residue of active chymotrypsin and dilute same.

(6) The lens is now luxated as the pupil contracts and the anterior chamber becomes deeper.

(7) The ventosa or erysiphake is applied to the surface of the lens and a vacuometric suction of 350 mm. of mercury is produced. This is sufficient to grip the subluxated lens. The lens is then lifted out of sulcus over iris margin and rotated out of eye.

(8) Lens on ventosa is now applied to corneal surface and pressed to get wound in alignment and iris replaced.

(9) Pilocarpine nitras 2% is instilled to get contracted circular pupil.

(10) Two to four corneal scleral sutures are then placed and all tied.

(11) The anterior chamber is irrigated. Air is instilled.

(12) Conjunctival frill is replaced.

(13) Guttæ penicillini is instilled and the lids are closed.

(14) Post-operative dressing applied.

## Results and Conclusions

Latest report—Barraquer has employed it with excellent results in more than 150 cases I have personally used it in 22 cases of cataract extractions since April 22.

One congenital cataract in a boy aged 11 years had a successful extraction of a mature cataract. Vision reduced to P.L. Intracapsular extraction was done. Adhesion between posterior pole of cataract and anterior hyaloid surface of vitreous was anticipated. The final delivery of lens produced a herniation of vitreous body into wound, but after a few minutes the vitreous fell back into original position and wound was closed satisfactorily.

The senile cataracts were of all types—amber sclerosed, intumescent and immature.

Three cases of old iritis complicated by subsequent cataract were in the series. The usual technique of posterior synechiotomy via the peripheral iridectomy and iris pupillary section at opposite pole was done. After zonulolysis the cataracts were extracted smoothly by phacoerysis. Two glaucomatous eyes had successful lens extractions. There are three bilateral cataract extractions in my series.

*Post-operative.*—No reaction. Any residual blood in the anterior chamber seems to disappear more quickly.

My patients are ready for discharge at the end of seven days and temporary lenses are used or available at that time.

## REFERENCE

Northrop, J. H., Kunitz, R. M., and Herriott, R. M. (1948) Crystalline Enzymes. Columbia Biological Series, No. 12. 2nd ed. New York.

**Mr. P. McG. Moffatt** said he was one of the lucky people to whom Dr. Barraquer had sent alpha-chymotrypsin. He did not use it at first because he was not sure of the correct method of diluting it; there was some difficulty in working out the proportions to make a 1/5,000 solution. A short time afterwards he received a phial containing 2 mg. and 10 ml. of saline, which stimulated him to use the material, and he had been using it for a short time, in fact only for about ten days. In that time he had done six extractions using the Barraquer erysiphake attached to a rubber bulb which was filled with saline. He had used this erysiphake for a long time before using alpha-chymotrypsin.

His experience, 6 cases, was very limited, but he hoped to use this method consistently because it made the extractions very much easier.

**Mr. Cogan,** in reply to a question, said that the first experimental work was done in Barcelona on rabbits, and various solutions were tried. 1/5,000 alpha-chymotrypsin was used on the rabbit with no effect at all. The only chimpanzee they had was sent away for naughtiness, so they switched to the human eye.

In the experimental work a ring was put round the cornea, the cornea was cut away and the iris cut away, leaving a pretty section of the lens in its zonule. That was subjected to a slow drip for three minutes with the alpha-chymotrypsin until the exact solution was found. The 1/5,000 was found ideal for the zonule.

Professor G. Knight of the Royal Veterinary College, London, who was interested in animal surgery of cataracts, and particularly in alpha-chymotrypsin, was dealing with much the same age group as were included in our congenital groups. He was working with a group which was very much tougher than the one Mr. Cogan had worked with. It was understood he was getting results in animals on a solution of alpha-chymotrypsin.

**Mr. Dermot Pierse** said that he had used alpha-chymotrypsin in his last 9 cases of extraction and in no case had there been any trouble at all. In none of the 9 cases had he found it necessary to use any counter-pressure and the lens was lifted straight out without tumbling.

He further asked Mr. Cogan about the use of alpha-chymotrypsin in congenital cataracts and what was the earliest age at which it had been used.

**Mr. Cogan** replied that Dr. Barraquer said he had done two at 18 months and one at 3 years.

# Section of Dermatology

President—JOHN T. INGRAM, M.D., F.R.C.P.

[*April* 17, 1958, contd. from September *Proceedings*, p. 712]

The following cases were also shown:

**Early Yaws.**—Dr. J. BARROW (for Dr. C. S. NICOL and Dr. H. J. WALLACE).

Boy aged 10, from Dominica, developed an ulcer on his ankle and some weeks later crusted papules appeared on scalp and trunk. *T. pertenue* was demonstrated in the serum from one of these lesions. Price's precipitation reaction and Reiter's protein complement-fixation test were positive in the blood. The condition responded quickly to treatment with penicillin. (Full report to appear in the *British Medical Journal*.)

**Warty Nævus.**—Dr. E. A. CRONIN (for Dr. H. J. WALLACE).

**Connective Tissue Nævus, Without Histological Abnormality, Occurring in Two Brothers.**—Dr. D. C. G. BETT (for Dr. H. T. H. WILSON).

**Linear Scleroderma Circumscriptum: Sclérodermie en Bandes.**—Dr. E. SKLARZ.

14-year-old girl. Skin condition dates from 1954, following virus pneumonia; affecting typically left shoulder and arm down to radial half of hand and fingers. Marked atrophy of muscles in these areas. Curious swelling on left side of upper part of sternum (X-rays negative): ? hitherto unknown symptom or ? Tietze's syndrome. X-ray examination: spina bifida occulta; alimentary tract normal. Vitamin E: no effect; now improving under systemic prednisolone.

**Widespread Irradiation Changes** (including areas of radionecrosis and Bowen's disease) with sclerodermatous infiltration of the legs following X-ray treatment for hirsuties.—Dr. B. SCHWARTZ.

**Pityriasis Lichenoides Chronica** in a man aged 42, of seventeen years' duration. General examination and investigations negative.—Dr. JOHN EVERALL (for Dr. G. B. MITCHELL-HEGGS).

[*May* 15, 1958]

**Lupoid Rosacea.**—BRIAN F. RUSSELL, F.R.C.P.

Mrs. M. M., aged 29, 4 children.

*History.*—At age 23, during second pregnancy, developed purplish discoloration of upper lip and nose with sore and itchy white spots; worse in cold weather.

*On examination.*—Diffuse purple discoloration of distal two-thirds of nose with fleshy papulation and slight scaling. Skin-coloured and brownish firm nodules on right side of chest, right arm, right knee and right ankle, the lesion near the knee having a central depression.

A tentative diagnosis was made of sarcoidosis, of lupus pernio type, but histology of the lesion on the shoulder revealed histiocytoma.

*Investigations.*—E.S.R. 3 mm. in one hour (Westergren). Hb 76%. Mantoux reaction weakly positive 1 : 10,000. W.R. and Kahn reactions negative. X-ray of chest clear.

Microscopic examination of material from nose: 7 demodices found in the contents of five follicles.

*Histology* from nose (Dr. H. Haber): Sarcoidosis can be excluded. The histology is compatible with rosaceous tuberculide.

Serum proteins: Total 4·5, albumin 2·3, globulin 2·2 g.%.

Dr. **Louis Forman:** It is well known that the *Demodex folliculorum* is a frequent inhabitant of the follicle in cases of papular and pustular rosacea. Some eight years ago Dr. M. Jessner in New York told me of his firm belief that the demodex was responsible for the follicular damage and inflammatory and pustular reaction in pustular rosacea. Since then I have been particularly interested in the examination of the contents of the pustules of rosacea. The mites are to be seen in a very high proportion of the pustules examined, sometimes in very large numbers. The mite may be actively motile, lying singly or in bundles of 3 or 4 or more. Again, I have seen small circular, oval and fusiform granular forms suggesting stages of development from larval to adult mites. I have been convinced that the mites, present constantly and in such numbers capable of penetrating into the

sebaceous glands, play a role in the folliculitis. There is a clinical variety of active rosacea, with a minimum of pustules but diffuse scaling and follicular hyperkeratosis. In two such patients I was amazed to find the scales swarming with mites of *Demodex folliculorum*, and again felt that they could well have been responsible for the follicular hyperkeratosis.

**Dr. C. H. Whittle:** Whitfield used to say that he liked to see patients with rosacea because they nearly always got well and I think he used sulphur, ung. sulphuris hypochloritis, which I still use with some success. I wonder if it is the sulphur acting on the demodex.

**Dr. I. Martin-Scott:** Some years ago I saw a young woman with a light brown papular and also follicular eruption around the muzzle area. Various investigations were negative, so I finally did a biopsy which showed the lanugo follicles choked with demodex. Feeling that this might well be the cause I treated her with Eurax cream to kill the mites, and the eruption cleared rapidly. In this single case I assumed that the demodex was pathogenic.

**Tuberculosis Verrucosa Cutis (? Waterborne Acid-fast Bacillus Infection).**—J. S. PEGUM, M.D.

D. I. male, aged 48. Breeder of tropical fish.

*History.*—Fourteen months' eruption on knuckles of hands, persistent with no tendency to heal.

*On examination.*—Raised red warty infiltrated lesions, covered in part with scale, over knuckles of both hands. No lymphadenopathy.

*Biopsy of skin of left knuckle.*—Hyperkeratosis, parakeratosis, keratotic and purulent follicular plugging, irregular acanthosis. Dermal infiltration with lymphocytes and a small aggregation of epithelioid cells. No acid-fast bacilli or fungi seen.

*Culture of biopsy material.*—At 37° C.: sterile. At room temperature (20° to 25° C.): acid-fast bacilli grown.

Guinea-pig inoculation: The organism produced no lesion in the guinea-pig, but has produced lesions in a mouse's tail.

Tuberculin reactions: 1 : 10,000 positive.

X-ray of chest: No active pulmonary focus seen.

*Comment.*—There are two interesting points about this case. Firstly, his occupation: he breeds tropical fish and in order to keep the water clear provides infusoria (unicellular protozoa) which he obtains from a separate tank in which he breeds snails. The snails are, he says, dirty creatures with a high mortality. Secondly, the acid-fast organism which Dr. J. Perrin has grown from the biopsy material: this grew at room temperature (approximately 25° C.) but not at 37° C.

There are three possibilities:

(1) That this is the ordinary human or bovine type of tuberculosis verrucosa cutis and that the organism grown at room temperature is coincidental and of no significance.

(2) That the condition is an infection with *Mycobacterium balnei* (Linnell and Norden, 1954).

(3) That it is an infection with another acid-fast organism derived either from fish or from snails.

Dr. Perrin is endeavouring to type the organism.

REFERENCE.—LINNELL, F., and NORDEN, A. (1954) *Acta tuberc. scand.*, Suppl. 33.

**Dr. Brian Russell:** Three types of swimming-bath granulomata have been described: true tuberculosis verrucosa cutis; cases due to *Mycobacterium balnei*; and other cases in which no organism is recovered and which are thought to be silica granulomata.

**Eosinophilic Granuloma of the Face of the Erythema Elevatum Diutinum Type.**—I. SARKANY, M.R.C.P. (for LOUIS FORMAN, M.D., F.R.C.P.).

Mr. F. K., aged 54, a children's entertainer.

*History.*—For three years this man has been aware of the presence of two purplish infiltrated plaques on the right side of his face and a similar lesion on the left side. About three to four months ago, a new lesion appeared on the left side of his chin.

*On examination.*—There are four purplish, irregularly shaped, raised plaques on the face. The most recent lesion on the left side of the chin is similar in appearance but smaller in size. Systemic examination is negative. The blood pressure is 160/100.

*Investigations.*—Hb 108%. E.S.R. 6 mm. in one hour (Wintrobe). W.B.C. 9,400 (polys. 64%, eosinos. 5%, lymphos. 27%, monos. 3%, basos. 1%).

*Histology* (Dr. H. Haber).—The epidermis shows acanthosis. Within the cutis, there is a marked granuloma arranged around patulous vessels consisting of round cells, histiocytes and a few eosinophils. The changes are situated within the mid-cutis and the fat tissue is not involved in the process.

**Dr. H. R. Vickers:** How important is the presence of eosinophils in this type of case? I had a case a few months ago and we have not found any eosinophils in the section.

**Dr. H. Haber:** The older the case the fewer eosinophils you will find.

**The President:** We have had one case with multiple lesions on the face which responded remarkably to chloroquine but we have had many which did not respond to anything.

The following cases were also shown:

**Epidermolysis Bullosa (Acquired).**—Dr. BRIAN F. RUSSELL.
**? Hypertrophic Lupus Erythematosus.**—Dr. CLIFFORD D. EVANS.
**Acne Agminata.**—Dr. W. FRAIN-BELL (for Dr. F. RAY BETTLEY).
**Case for Diagnosis ? Incontinentia Pigmenti.**—Dr. J. H. ALLISON.
**Dermatitis Repens and Psoriasis.**—Dr. I. MARTIN-SCOTT.
**(1) Hansen's Disease simulating Lupus Vulgaris. (2) Pityriasis Rubra Pilaris.**—Dr. J. SCOPES (for Dr. R. T. BRAIN).
**Darier's Disease to show Effects of Dermabrasion.**—Dr. D. A. LARNDER (for Dr. S. C. GOLD).
**Hypergammaglobulinæmia (? Reticulosarcoma ? Myelomatosis) presenting with Pruritus and Ichthyosis.**—Dr. C. M. RIDLEY.
**Juvenile Dermatitis Herpetiformis.**—Dr. I. SARKANY (for Dr. L. FORMAN).
**Turban Tumour.**—Dr. R. G. HOWELL and Dr. S. BERNSTEIN.

Dr. F. F. HELLIER read a paper entitled **Primary Systematized Amyloidosis with Striking Skin Changes.**

[*June* 7, 1958]

## MEETING AT THE GENERAL INFIRMARY, LEEDS

**Madura Foot (Mycetoma).**—S. T. ANNING, M.D., F.R.C.P.

E. J., male, aged 27. Labourer.

*History.*—A West Indian negro. In this country one year. Formerly a bare-footed fisherman living on a wooded island. Injured left foot at age of 15 years (probably on a wood splinter). Painful swelling of foot in region of old injury appeared three months ago.

*Clinical findings.*—Granulomatous, indurated lesion on lateral aspect of left foot with some ulceration about 6 × 5 cm. in area. General examination normal apart from keloid on front of chest.

*Investigations.*—Wassermann reaction negative.

Biopsy: The tissue was very tough on cutting and small black grains were visible in the dermis. The section shows a pyogenic inflammatory reaction with occasional giant cells. A granule of dense, thick-walled mycelium was present within an abscess cavity.

X-ray of foot: A minor congenital abnormality of the bones was seen, but no evidence of invasion of bone by the disease.

Mycology: Growth of *Madurella grisea.*

*Discussion.*—**Dr. C. J. P. La Touche** reported that the fungus was identified and described in 1948 by Mackinnon *et al.* from 5 cases in South America. 3 other cases from South America have been recorded, as well as single cases from U.S.A., Belgian Congo and Senegal.

**Dr. H. Haber** and **Dr. A. Bigham** confirmed that good response had been seen in India from penicillin.

**Lymphocytic Lymphoma.**—J. T. INGRAM, M.D., F.R.C.P.

D. A., female, aged 58. Housewife.

*History.*—July 1956: Nose red and infiltrated. December 1956: Right ear lobe affected. By June 1957 the nose and both ear lobes were red and swollen. Following treatment with calciferol she developed small nodular infiltrations of lacrimal glands, under skin of cheeks and under jaw. Posterior cervical glands palpable.

*Clinical findings.*—Infiltration of skin of nose and ears and of subcutaneous tissues of cheeks, eyelids and neck and of cervical glands.

*Investigations.*—X-ray: Lungs clear. No bone changes in hands suggestive of sarcoid but some arthritic changes.

Blood: E.S.R. 119 mm. in one hour (Westergren). R.B.C. 3,790,000. W.B.C. 7,900, normal differential. Serum proteins: Total 8·5, albumin 4·2, globulin 4·3 g.%. Blood urea nitrogen 19·6, serum calcium 9·6 mg.%.

Histology of a subcutaneous nodule shows dense infiltration of lymphocytes without germ-centres, although some appear immature. Appearance suggests lymphocytic lymphoma or lymphosarcoma. Histology of the ear is exactly similar.

*Discussion.*—**The President** noted that a confident diagnosis of sarcoidosis had been made originally but histology showed a lymphocytic lymphoma or lymphosarcoma. Bone marrow had not been examined.

**Elastoma Intrapapillare Perforans Verruciforme (Miescher).**—S. T. ANNING, M.D., F.R.C.P.

G. B., male, aged 18.

*History*, 1955.—Papules on nape of neck one year. Scaling patches on wrists, forearms and forehead intermittently for several years. No relevant family history.

*Clinical findings*, 1955.—Papules scattered in groups chiefly on left side of nape and arranged in annular and gyrate patterns. Papules have a slightly hyperkeratotic surface. A few similar papules splashed on radial aspect of wrists. Scaling patch (like pityriasis alba) right temple. A little oil acne on thighs (oily work in engineering).

*Investigations*, 1955.—Biopsy of papule on nape: histological examination confirmed the diagnosis.

*History*, 1957.—Admitted November 10, 1957, under Dr. J. R. H. Towers after sudden collapse. Died in a few hours. Autopsy showed dissecting aneurysm with multiple tears of the aorta, which was thin-walled. Histological examination of aorta: degenerative elastic tissue.

**Lupus Erythematosus (Profundus).**—J. T. INGRAM, M.D., F.R.C.P.

L. K., female, aged 39. Housewife.



FIG. 1.—Lupus erythematosus with depressed scarring and atrophy resembling lipodystrophy.

*History.*—Started with L.E. on right side of nose in spring of 1945. The lesion extended over a bat's-wing distribution on forehead and cheeks, with subcutaneous atrophy. 1951: A dusky discoloration with induration was present about and beyond the lesions. A subcutaneous nodule was present in the submandibular region and another on the left upper arm. The face progressed to extreme atrophy and scarring with infiltration peripherally (Fig. 1). General health has remained good.

Past history and family history and general examination revealed nothing of note.

*Clinical findings.*—Induration has now almost cleared. No evidence of systemic lupus erythematosus. Blood pressure 130/90.

*Investigations.*—X-rays: Chest: Calcified nodes left hilum, left paratracheal region and both axillæ; no active lung lesion. Facial bones normal. Sinuses clear.

Wassermann reaction negative. Mantoux 1 : 10,000 positive. Hb 90%. R.B.C. 4,700,000. W.B.C. 5,900, normal differential. E.S.R. 46 mm. in one hour (Westergren). Blood urea nitrogen 18 mg.%.

Biopsy from nasolabial fold: Hyperkeratosis. No liquefactive degeneration of basal layer. Large infiltrations of lymphocytes around blood vessels in deeper dermis and subcutaneous fat but no cellular infiltrate in the upper corium.

*Treatment.*—Bismuth. Gold. Antihistamines. Mepacrine. Sterogyl. Rimifon. No internal treatment for past year.

*Discussion.*—**Dr. P. J. Hare** thought there was lipodystrophy as well as lupus erythematosus.

**Dr. R. P. Warin** recalled that he published with the President a case of lipodystrophy with lupus erythematosus of the nose (Warin and Ingram, 1950, *Lancet*, ii, 55).

**Dr. Brian Russell** had a patient with lipodystrophy who had developed lupus erythematosus in the past two years.

**Case for Diagnosis. ? Poikiloderma in a Baby.**—F. F. HELLIER, O.B.E., F.R.C.P.

A. M., male, aged 12 months.

*History.*—Since two months old an extensive rash. No family history of this. Two other children normal.

*Clinical findings.*—A dusky red confluent eruption of the limbs, but sparing the elbows and knee bends, sharply defined. In many places there are white round glazed areas in the rash. The face is red and shiny with some blotchy, almost telangiectatic, lesions. No teeth yet, and although he is now a year old he is not making any effort to walk.

*Discussion.*—Some members suggested Thomson's poikiloderma but **Dr. D. I. Williams** did not agree.

Dr. M. **Feiwel** suggested Rothmund's syndrome and **Dr. F. G. Sherry-Dottridge** noted the white eyelashes.

The **President** thought there might be a question of underlying systemic disease such as polyarteritis or reticulosis.

**Poikiloderma and Pigmented Lichen Sclerosus (Lupus Erythematosus).**—J. T. INGRAM, M.D., F.R.C.P.

E. T., female, aged 61. Housewife.

*History.*—Poikilodermatous lesions about breasts and abdomen, and areas of atrophy and telangiectasia surrounded by dense pigmentation about anus and groins with some pruritus. Onset autumn 1956. Recent symmetrical erythema on face and V of neck and forearms resembling lupus erythematosus clinically and histologically. Right eye removed seven years ago for glaucoma. Hypertension. Blood pressure 230/135; has had slight seizure. Menopause at 52 years.

*Clinical findings.*—Poikiloderma on flanks, abdomen, breasts, lower legs, pubic area and groins. Atrophy and pigmentation at anus and in groins resembling X-ray scarring. Facial rash has cleared on Nivaquine.

*Investigations.*—Blood picture and erythrocyte sedimentation rate normal. No L.E. cells. Serum proteins 6·9, albumin 4·0, globulin 2·9 g.%. Blood urea nitrogen 30·1 mg.%. Urea clearance test 52%. Urea concentration test normal. Urine: no porphyrins found. Candida in scrapings from groin.

Histology.—Perianal skin: Thickening of horny layer. Interpapillary processes of the epithelium are much attenuated. The superficial corium is rather vascular and fibrous and shows perivascular lymphocytic infiltration. Left wrist: Hyperkeratosis and parakeratosis and some flattening of the pegs and liquefaction of basal layer. There is some prominence of the dermal vessels with scanty infiltration.

*Treatment.*—Hydrocortisone and nystatin ointments. Nivaquine 200 mg. b.d.

*Discussion.*—**Dr. R. E. Church** had a patient with lichen sclerosus showing similar poikilodermatous changes.

POSTSCRIPT.—The whole affection has now cleared dramatically suggesting the single diagnosis of lupus erythematosus.

The following cases were also shown:

**Maffucci's Syndrome. Hypertension.**—Dr. M. MALDEN (for Dr. R. E. CHURCH).

**Candidiasis.**—Dr. A. J. E. BARLOW.

**Spontaneous Hypoparathyroidism with Generalized Moniliasis in a Boy of 14 Years.**—Dr. S. T. ANNING.

**? Connective Tissue Nævus.**—Dr. F. F. HELLIER.

**Kaposi's Idiopathic Sarcoma.**—Dr. J. T. INGRAM.
Male, aged 77. Father a Polish Jew. Twenty years' duration and showing cystic lesions (lymphangiectatic).

**Steatocystoma Multiplex with Embryonal Hair Formation.**—Dr. CLIFFORD E. STUART.

(1) **Pressure Urticaria.** (2) **Red Urticaria. ? Mastocytosis.** (3) **Scleroderma.**—Dr. F. F. HELLIER.

**Case for Diagnosis.**—Dr. J. SAVAGE.
Female aged 7 with chronic granulomatous lesions on the skin.

**Psoriasis.**—Dr. J. T. INGRAM.
Male, aged 63. To show dramatic, temporary effect of Ledercort.

**Lichen Planus with Scarring and Blistering.**—Dr. F. F. HELLIER.

**Reticulum Cell Sarcoma.**—Dr. J. T. INGRAM.
Male, aged 61. Solitary lesion of right cheek of five months' duration with tendency to plasma-cell differentiation. No bone lesions.

**Purpura and Parapsoriasis.**—Dr. J. T. INGRAM.
Female, aged 60. Purpura for forty-five years, parapsoriasis for twelve years.

**Polyarteritis Nodosa.**—Dr. R. H. SEVILLE and Dr. J. T. INGRAM.
Male, aged 46. Mostly cutaneous with livedo of twelve years' duration but positive muscle biopsy. Dysproteinæmia approaching macroglobulinæmia.

The following papers were read:

**The Advance of Molecular Biology.**—Professor W. T. ASTBURY, F.R.S.

**Tuberculosis of the Skin, Social Aspects.**—Professor GUSTAV RIEHL.

[*June* 26, 1958]

**Polymyositis and Thyroiditis.**—DENIS SHARVILL, M.R.C.P.

Miss L. S., aged 55.

*History.*—Rheumatoid arthritis for many years; several admissions to hospitals and spas. Hæmatemesis once and malæna twice in 1954, attributed to acute gastric and duodenal ulcers.

*Present illness.*—Skin changes appeared in early April 1958, consisting of: (1) Dusky erythema and minimal fine scaling of the upper eyelids and of the sides of the nose, with a few telangiectases. (2) An annular eruption of the front of the neck, consisting of a narrow band of atrophy, telangiectasia and scaling. (3) Erythema and swelling of the finger nail-folds, with sero-sanguineous discharge. (4) Pin-head-sized purpuric spots of the finger tips. (5) A scaly erythematous disc on the right knee. (6) Psoriasiform lesions of the buttocks, which later became decubitus ulcers. Her general condition seemed fair, except for arthritis of most joints, but she remarked on difficulty in swallowing "due to mucus in the throat". Although at this time the general weakness seemed no more than could be accounted for by the arthritis, the dysphagia and pleomorphic skin lesions suggested the diagnosis of polymyositis, and during the three weeks following admission to hospital muscle weakness became profound, especially proximally. Finally she could only swallow sips of fluid; she could not sit up or raise her arms sufficiently to feed herself, or raise her knees from the bed. She appeared moribund. For two weeks she had taken Plaquenil (hydroxychloroquine) 400 mg. b.i.d.; during this time the skin lesions had disappeared except for those on her buttocks. In searching for a possible neoplasm a nodule was felt deep under the left sternomastoid; although its clinical features were indefinite it was certainly arising from the thyroid. With some misgivings because of her general condition it was decided to explore the thyroid.

*Operation* 9.5.58 (Mr. Rex Hunter).—The thyroid was bilaterally enlarged, hard and knobbly; much of it was retrosternal. In view of apparent malignancy total thyroidectomy was performed. It did not appear that the gland was causing significant obstruction.

*Progress.*—It was hardly expected that the patient would survive operation, but twenty-four hours later she remarked that she felt much better and that swallowing was easier; subsequently she steadily improved. She now has some power in her arms and legs and no difficulty in swallowing. She can feed herself, and has walked eighteen steps with assistance. She notices that the pain in the arthritic joints is less than for years. There is still profound atrophy of muscles, particularly of the arms and thighs. There is atrophy of the skin on the backs of the hands and wrists, and on the chest; although widespread this is not gross. The deep and extensive bedsores have almost healed. She is taking thyroid ½ gr. t.i.d. and iron. She has been given further Plaquenil, and Nilevar (norethandrolone) since operation, but these have been discontinued. At no time has she received corticotrophin or corticosteroids.

*Investigations.*—Extensive radiological and pathological investigations were carried out on several occasions. No evidence of neoplasm was found. All results were in keeping with the diagnosis of polymyositis.

Positive findings: E.S.R. over 100 mm. in the first hour (Westergren). Serum proteins: 6·2–7·5 grams/100 ml., globulin 72–77% of total, γ-globulin up to 50% of total protein by paper electrophoresis. Thyroid antibodies demonstrated in diagnostic titre (Dr. A. C. Cunliffe, Department of Bacteriology, King's College Hospital). Urine: Creatine excretion 300 to 500 mg. in twenty-four hours. Leucine, glycine and alanine demonstrated by paper chromatography. No myoglobin detected. Histology: Muscle (deltoid, sternomastoid and infrahyoid) showed all the described changes of polymyositis. Thyroid showed a picture of acute thyroiditis (Hashimoto).

*Postscript* (16.8.58).—Clinical improvement has been maintained and she has been discharged from hospital, still very weak but able to get about the house. This clinical improvement has not been accompanied as yet by significant improvement in pathological abnormalities.

*Comments.*—The association of polymyositis with thyroiditis of the Hashimoto type does not appear to have been described in the literature, although there have been references to a possible relationship of thyrotoxicosis to polymyositis; this is not generally accepted (Walton and Adams, 1958). This is an interesting conjunction of rare diseases with several noteworthy features: (1) The striking similarity between the cellular infiltrates in the thyroid gland and in the muscles. (2) The remarkable and immediate improvement in the patient's condition following total thyroidectomy. (3) The fact that both these diseases are of unknown ætiology, and both associated with the formation of auto-antibodies.

REFERENCE.—WALTON, J. N., and ADAMS, R. D. (1958) Polymyositis. Edinburgh and London.

**Scleroderma and Carcinoma.**—LOUIS FORMAN, M.D., F.R.C.P., and HEDLEY ATKINS, M.Ch.

I. C., female, aged 52. Organist.

July 1957: Alternate diarrhœa and constipation.

December 1957: The hands became clumsy; the skin of the hands thickened, and this process has progressed to involve the arms and the feet. There has been no weakness of the neck, shoulder or pelvic girdle muscles or difficulty in swallowing.

February 1958: Abdomino-perineal resection of the rectum (Mr. Hedley Atkins). The rectum was the site of an adenocarcinoma which infiltrated the perirectal fat. The lymphatic glands appeared free of growth. The liver was free of growth by palpation at operation.

*Clinical findings.*—The skin of the left side of the face and neck and over the sternum shows changes of an involuting scleroderma. The left side of the neck is yellow and irregularly thickened. The forearms are pigmented, the skin rigid and shiny. The hands show rigidity of the skin over the dorsal and ventral aspects and the fingers are affected similarly, and are contracted. The lower legs and feet are affected. No weakness of the musculature can be demonstrated. The hand grip is weak but this is probably due to the induration of the skin and deep cutis. An unusual and unexplained finding is the elevated temperature of the hands and feet indicating an increased peripheral blood flow.

*Investigations.*—Biopsy of forearm: Epidermis shows pigmentation of basal layer. In places there is a degree of papillomatosis and acanthosis recalling acanthosis nigricans. The cutis is much thickened; the upper half œdematous, collagen fibres being disintegrated; the fibres in the deep cutis are thick and closely approximated. Some of the vessels are cuffed with lymphocytes. The elastic tissue is well preserved. Biopsy of skin of neck: œdema and disintegration of the collagen is marked in a band just below the epidermis, the collagen bundles elsewhere being thick and closely approximated. The elastic fibres are well preserved.

*Comment.*—The association of scleroderma and malignancy is uncommon and hence most authors have suggested that it is accidental. I observed a case under the care of the late Dr. H. W. Barber, of generalized scleroderma with carcinoma of the ovaries. Curth (1955) illustrated a case of localized scleroderma in a woman suffering from recurrent epidermoid cancer of the cervix.

Christianson *et al.* (1956) reviewed 125 patients with generalized scleroderma, 8 of whom, 7 females and 1 male, had an associated carcinoma. Increasing attention has been given to the possibility of auto-immune bodies being formed by a cancerous tumour, or by the host to the cancer cells, and this state of auto-sensitization might in some instances lead to the degenerative changes of ground substance and collagen resulting in scleroderma.

REFERENCES

CHRISTIANSON, H. B., BRUNSTING, L. A., and PERRY, H. O. (1956) *Arch. Derm. Syph., Chicago,* **74,** 581.

CURTH, H. O. (1955) *Arch. Derm. Syph., Chicago,* **71,** 106.

**The President:** I would like to feel that there was some relationship between the carcinoma of rectum and the scleroderma here but it is uncertain. I do not know why there should be increased blood flow through the hands and feet. This is in my opinion a case of scleroderma of the morphœa type though diffuse and is not acrosclerosis or systemic sclerosis.

**Dr. G. B. Dowling:** I class this case as a scleroderma of the diffuse or disseminated morphœa type and not the Raynaud's type. One would not expect to find the visceral changes of scleroderma in this class of case. Where the carcinoma comes into it I do not know.

**Besnier's Prurigo with Calcinosis.**—BRIAN RUSSELL, M.D., F.R.C.P.

C. B., male, aged 38. Salesman.

*History.*—Infantile eczema followed by Besnier's prurigo. Two and a half years ago he was treated with 100 mg. of cortisone daily for three weeks. For the last twenty-one months he has been treated with prednisolone, the maintenance dose being 10 mg. daily. For eight months aching pains in fingers and feet, followed by development of white nodules in fingers and conjunctivæ. For a few weeks palpitations, thirst and increased nocturnal frequency of micturition.

*Clinical findings.*—Xeroderma. Terracotta facies with broken eyebrows. Diffuse yellowish-brown pigmentation of skin. Antecubital and popliteal lichenification. White dermographism. Onychophagia. White nodules in bulbar conjunctiva. Irregular, firm white nodulation of right middle and ring fingers.

Blood pressure 140/80. Urine sp. gr. 1008. Trace of albumin. A few leucocytes and red cells present.

*Investigations.*—Blood: E.S.R. (Westergren) 115 mm. in the first hour. Hb 49%. W.B.C. 21,300 (polys. 73%, eosinos. 4%, lymphos. 21%, monos. 2%). Blood urea 138 mg. per 100 ml. Urea clearance 6%. Blood uric acid 3·6 mg. per 100 ml. Serum cholesterol 235 mg. per 100 ml. Total plasma proteins 7·1 grams per 100 ml. (albumin 4·7; globulin 2·4). Serum protein electrophoresis normal. Plasma chloride (as sodium chloride) 515, sodium 308, potassium 24 mg. per 100 ml. Serum calcium 16·4, phosphorus 5·1 mg. per 100 ml., alkaline phosphatase 4 King-Armstrong units.

Sternal puncture: Normal bone-marrow; no excess of plasma cells.

Urine: Bence Jones protein present. Ureteric catheterization: a few leucocytes and red cells from right side only. Pyelogram: no excretion of dye seen. Retrograde pyelogram: no abnormality in pelves or calyces.

X-ray reports: Skull: no evidence of myelomatosis. Long bones: no osteoporosis. Fingers: opaque material in soft tissues. Abdomen: no renal calcification.

Material from incised nodule: Calcium phosphate.

*Progress.*—Following blood transfusions the hæmoglobin is now 78%. The low sodium state has been corrected. He is now taking prednisone and iron.

**Dr. M. Feiwel:** In some respects the appearance of the fingers with their deposits of calcium is more reminiscent of calcinosis of the circumscripta type which is unassociated with any abnormality of calcium metabolism. The patient, however, has hypercalcæmia with metastatic calcification which is usually due to hyperparathyroidism whether primary or secondary from renal disease as in this patient or to hypervitaminosis D.

In the absence, as yet, of certainty as to the cause of the patient's renal pathology it is conceivable that one morbid process by damaging both the peripheral tissues and the kidneys might produce the two types of calcification in the one patient, namely "collagen" disease.

**Dr. Brian Russell:** The investigations indicate metastatic calcinosis resulting from a pathological process in the kidneys rather than in the parathyroids. A congenital anomaly of the renal tract has been suggested. The Bence-Jones proteinuria is unaccompanied by X-ray or cytological evidence of myelomatosis and the serum proteins are normal.

**Dr. G. C. Wells:** It seems that this hypercalcæmia is likely to be renal in origin, if parathyroid disease has been excluded. Sarcoidosis might just be considered as a rare cause of hypercalcæmia and uræmia. Its importance is related to the good response derived from cortisone, provided renal damage has not advanced too far.

ADDENDUM (16.10.58).—When the sodium deficiency was corrected the serum calcium returned to normal and remained normal for two months although it has now risen again to 13·8 mg.%. The signs of calcinosis on the digits have entirely disappeared though the white plaques in bulbar conjunctivæ persist. The blood urea remains high (90 mg.%) and the anæmia persists (Hb. 60%). There is now slight potassium deficiency.

It has been suggested that the patient has a salt-losing renal lesion. She has had no therapeutic measures which might have produced it. Prolonged treatment with prednisone of a patient with impaired renal function may, however, have been responsible for the calcinosis.—B. R.

The following cases were also shown:

**Eruptive Papular Reticulo-granuloma.**—Dr. R. E. CHURCH.

(1) **? Chronic Moniliasis of the Mouth.** (2) **Pemphigus vegetans with Severe Involvement of Mouth.** (3) **? Late Specific Eruption with Morphology and Histology of Granuloma Annulare.**—Dr. LOUIS FORMAN.

**? Pityriasis Rubra Pilaris. ? Ichthyosiform Erythrodermia. Hydrocephalus. Vitamin-A Intoxication.**—Dr. F. RAY BETTLEY and Dr. BRIAN RUSSELL.

(1) **Pityriasis Rubra Pilaris.** (2) **? Lymphœdema.** (3) **Scaling of Palms and Soles (for Diagnosis).** (4) **? Kerato-acanthoma.**—Dr. E. J. MOYNAHAN.

**Keratosis Follicularis Serpiginosa (Lutz) (or Elastoma Intrapapillare Perforans Verruciforme (Miescher)).**—Dr. D. S. WILKINSON.

Case showing rather extensive lesions on neck and cheeks, evolving for a year in a Mongol aged 10. Characteristic histology.

**Leucoderma Centrifugum Acquisitum (Sutton).**—Dr. M. GARRETTS (for Dr. W. N. GOLDSMITH).

(1) **Hypercholesteræmic Xanthomatosis Clinically Resembling Normocholesteræmic Xanthoma Disseminatum.** (2) **Sarcoidosis with Lesions Resembling Necrobiosis.**—Dr. PETER SMITH (for Dr. BRIAN RUSSELL).

**Cutaneous Leishmaniasis.**—Dr. P. MONTGOMERY (for Dr. E. J. MOYNAHAN).

**Necrobiosis Lipoidica Diabeticorum.**—Dr. V. WILSON (for Dr. E. J. MOYNAHAN).

**Weber-Christian Disease in a Child of 4 Years Old.**—Dr. M. E. EILOART (for Dr. G. F. MITCHELL-HEGGS).

Dr. J. G. HOLMES gave a photographic demonstration on **Herpes Simplex Causing Conjunctivitis Without Keratitis.** Spontaneous remission is usual. Local or systemic steroid therapy is contra-indicated.

# Section of Psychiatry

President—Professor E. STENGEL, M.D., M.R.C.P.

[*April* 8, 1958]

## The Post-operative Psychoses [*Summary*][1]

By B. B. ZEITLYN, M.D., D.P.M.
*Cambridge*

THIS paper presents the results of a study undertaken jointly with Professor E. Stengel and Mr. E. Rayner.

The term "post-operative psychoses" refers to mental illnesses which follow in the wake of surgical operations. These conditions have received but little attention from psychiatrists, while the psychiatric textbooks either do not mention them or consider them usually with the delirious or toxic-exhaustive states.

The early psychiatric literature emphasized the role in ætiology of constitutional predisposition, infection, anæsthetics and antiseptics, but the surgeons and gynæcologists—for example, Dent (1889)—emphasized the importance of the dread of operation, and the worries and anxieties associated with it. Kleist (1916) gave the name "Interval Psychosis" to the many cases where a latent interval occurred between the operation and the onset of the psychosis, in contrast to the post-anæsthetic and the organic psychoses which were alleged to follow immediately upon the operation.

Anæsthetics have for long been blamed for the post-operative psychoses which can, however, occur when no anæsthetic at all is used. The post-anæsthetic syndrome is further distinguished by its characteristic clinical picture. Together with such symptoms as confusion and coma, there occur signs of local involvement of the central nervous system, due to selective anoxia.

The site of the operation has also been regarded as important in the ætiology of post-operative psychosis. Apart from the proclivity of eye operations to this sequel, due in part to bandaging of the eyes, especially in patients over 60, gynæcological operations have been thought to be especially liable to psychological complications. However, the question has been raised as to whether or not it is the age of the patient rather than the site of operation which is the risk-carrying factor.

It is most commonly held that organic reaction types usually constitute a post-operative psychosis. The belief persists that the post-operative syndrome is a specific one, and special types of excitement and elation have been reported (Muncie, 1934; McDermott and Cobb, 1938).

### *Present Study*

We could deal only with those reactions to operation severe enough to require admission to a psychiatric hospital and particularly to an observation ward. Neurotic and the milder psychotic reactions were therefore largely excluded. The 80 patients in the series, 58 females and 22 males, were studied as to their representativeness according to the hospitals from which they derived. Despite the wide range of operations encountered, the predominance of females and the seemingly high proportion of gynæcological operations was noteworthy.

In no case could one say that the anæsthetic precipitated the psychosis. That is to say, in no case were the signs and symptoms of the post-anæsthetic syndrome observed.

[1] For full paper *see J. ment. Sci.*, 1958, **108**, 389.

The type of reaction found was affective in 46 cases, schizophrenic in 12, and confusional in all but one (neurotic reaction) of the rest. In the confusional category, only the cases associated with dementia or heart failure occurred immediately after surgery, and in the majority the latent interval was from six to fourteen days.

Symptoms conformed to those of the usual reaction types, although on occasion an element of perplexity coloured the picture; while in 4 cases confusion in the acute stages subsequently cleared to give the characteristic features of the depressive or schizophrenic reaction types.

No consistent response to successive operations was noted. In some cases each surgical intervention was followed by psychosis, but more usually, while one operation had this result, others both before and afterwards had no such sequel.

An attempt to examine those factors possibly influencing proneness to post-operative breakdown led to the analysis for control purposes of 1,539 operations on males, and 3,356 on females. Further control samples from the observation ward and from a mental hospital were used in the study, which showed, for example, that neither sex is indeed more prone to mental illness after operation. Likewise no significant difference exists between the male : female ratio in post-operative psychoses and in psychoses generally. We were able to confirm that women do in fact become more liable to this complication with increasing age—an age tendency, however, found also in mental hospital and observation ward populations.

There was no evidence to suggest that abdominal or gynæcological operations are more likely than others to be followed by psychosis, but hysterectomy would appear to carry a greater risk than other gynæcological operations. Of the possible explanations for this, the importance of the age factor here could be seen.

The incidence of the various psychotic reaction types in the series matched that found in the observation ward, except that the frequency of schizophrenia was found to be significantly less than would be expected from the trend of psychoses generally.

In conclusion it can be said that there is no evidence for the existence of an entity "post-operative psychosis". Its clinical status is similar to that of puerperal psychosis which likewise has been shown to manifest itself in a variety of common reaction types. It is of interest in this connexion, that some patients in the series had a history of both a puerperal and a post-operative psychosis. Whether and what type of psychosis develops in an individual, depends on predisposing factors, while the operation or childbirth acts as the precipitating cause. The role of emotional factors, assumed to be important for both, remains uncertain at least as far as post-operative psychoses are concerned. Would then our patients have developed a psychosis if they had not had their operations? The answer is that they probably would not have had that psychosis at that particular time, but probably at some other occasion and precipitated by some other stressful event.

REFERENCES

DENT, C. T. (1889) *J. ment. Sci.*, **25**, 1.
KLEIST, K. (1916) Post-operative Psychoses. Berlin.
MCDERMOTT, N. T., and COBB, S. (1938) *Med. Clin. N. Amer.*, **22**, 569.
MUNCIE, W. (1934) *Arch. Neurol. Psychiat. Chicago*, **32**, 4.

[*May* 13, 1958]

# Clinical Studies in Psycho-analysis

## (Research Project of the Hampstead Child-Therapy Clinic)[1]

By ANNA FREUD, LL.D.

*London*

*Place of Research*

THE following is a brief and preliminary account of some clinical investigations which are being carried out by a group of people who co-operate in work in the Hampstead Child-Therapy Clinic. This group consists of a number of analysts and child-analysts, all of them members of the British Psycho-Analytic Society, supplemented by a number of analytic child-therapists who have qualified from the four years' training course which is attached to the Clinic. The Clinic itself has functioned since 1951 and has grown steadily since

[1]The Research Project of the Hampstead Clinic is financed by the following Foundations: The Field Foundation, Inc., New York; The Ford Foundation, New York; The Foundations' Fund for Research in Psychiatry, New Haven, Connecticut; The Grant Foundation, Inc., New York; The Psychoanalytic Foundation, New York.

then. At present, the number of people engaged in clinical work there stands somewhere between thirty and forty. Interest is directed on the one hand to the treatment of childhood disorders, on the other hand to the study of childhood development, normal and abnormal.

*The Question of Planned Research in Analysis*

Analysts have been reproached often for taking no interest in planned research and the methods serving it; of making their discoveries haphazardly and incidentally; of not choosing their material according to plan; of working as individuals and not in teams; and of allowing their case-material to drift out of sight without follow-up. All these failings exist, or have existed, but have to be attributed to the conditions of the past when psycho-analysis was wholly a matter of private practice and hedged in by the difficulties and restrictions imposed by the circumstances of the latter. It was these conditions which permitted no planned selection of cases, imposed limits on the undistorted publication of material and made the follow-ups dependent on the goodwill of the former patients. That a steady accumulation of findings was possible even under those conditions, unfavourable as they seem now, was due only to the lucky chance that in psycho-analysis the method of therapy is identical with the method of enquiry. This rare combination allowed for no routine work in analysis and conferred the potential of a research case on every patient who entered psycho-analysis for his private therapeutic purposes.

Conditions changed in this respect when psycho-analysts began to make contacts with established research centres and when the first psycho-analytic clinics were established. Examples of new research activities are reported in the literature. Interestingly enough, the earliest undertakings of this nature did not confine themselves to the field of psycho-analysis proper but explored the border lines, on the one hand between psycho-analysis and organic medicine, on the other hand between psycho-analysis and academic, genetic psychology. In both instances extraneous research techniques were either added to the analytic method or substituted for it for purposes of exactness. It remained an open and debated question whether research could be planned also to take place within analysis itself, on topics of purely analytic interest, carried out by analysts who employ the analytic method only, without sacrificing any part of it.

It is this latter question which the workers in the Hampstead Child-Therapy Clinic have set out to answer in the affirmative. It is still too early to report on the results of the research projects which are in progress; this will have to wait until the investigations are further advanced, or concluded, and brought into publishable form. The present intention is only to use these activities as examples and illustrations of the possibility of research within the analytic field. At the same time the question is being raised which devices may be used legitimately in an analytic clinic to operate research projects. Two such devices will be discussed: (*a*) the pooling of clinical material among a group of analytic workers; (*b*) the planned selection of cases; the contention being that the consistent employment of both, singly or in combination with each other, improves the conditions for fact-finding to a considerable degree and opens up new opportunities for evaluating, comparing and verifying data. Pooling of material and planned case-selection are used also to counteract disadvantages for research which are inherent in analytic work, such as the comparative absence of specialization and the impossibility of setting up experiments. Thus, the projects of the Clinic can be shown to have a double motivation. On the one hand they are aimed at increasing knowledge of mental processes and contents, and the techniques of handling them in therapy; on the other hand at eliminating or decreasing some of the most common handicaps under which analysts labour when they work privately, unaided and in isolation.

A. The Absence of Specialization in Analysis. Remedy by Pooling Material

A definite and directed search for material runs counter to the analytic technique according to which the analyst's attention should be free-floating and receptive for all the vagaries of the patients' associations and attitudes. Therefore, specialization, with its inevitable centering of attention on selected topics, is not encouraged in analytic training and practice, essential as it may be for research purposes in other branches of work. With exceptions, it remains rare for an analyst to treat simultaneously more than two or three cases of the same type and diagnosis, apart, of course, from the broader divisions into adult analysis, child-analysis, the analysis of delinquents or psychotics.

The remedy in clinic practice is a simple one. Instead of one analyst treating 8 to 10 cases of similar type simultaneously, 8 to 10 such patients are distributed among an equal number of analysts, their clinical material being shared by means of weekly and bi-monthly reports and compared weekly in a discussion group. This method intensifies typical features in contrast to individual ones and helps to minimize any subjective elements introduced into objective material by the persons, or variations of technique, of the individual analysts.

So far two projects of the Clinic have been based on this principle.

(i) *An Inquiry into the Analytic Treatment of Adolescents*
Number of analysts: 15. Patients: 15.

*Content and aim of project.*—There is among analysts a fair amount of consensus regarding the nature and range of the conscious and unconscious conflicts which underlie the neurotic or pre-psychotic upheavals of adolescence. In spite of this knowledge the technical handling of adolescents in analysis has remained a problem since neither the technique of child-analysis nor the technique for adults is wholly applicable. The technical tool of free association cannot be used in most cases, even common honesty, i.e. the sharing of conscious experience with the analyst usually remains incomplete. Heightened defences against irruptions from the unconscious render resistances impregnable in many cases. Transference tends to be acted out as with border-line and psychotic patients. Owing to these difficulties, adolescents break off treatment at unsuitable moments in far greater numbers than any other type of case. It is the aim of this study to establish by common effort the most typical features of the adolescent process and to base the necessary variations and adaptations of technique on them.

For further details of this project see the following preliminary report given by Dr. Ilse Hellman (*p.* 942).

(ii) *An Inquiry into the Analysis of Border-line Cases* (Age; latency and pre-adolescence)
Number of child-therapists: 9. Patients: 8.

*Content and aim of study.*—The material of these cases is reviewed and discussed especially from the aspect of (*a*) use of language and its distortion; (*b*) acting out of primitive impulses versus their verbalization; (*c*) the profusion of fantasy-life and its defensive use; (*d*) comparison of ego-functions and activities with those of normal or neurotic children; (*e*) the specific nature of the object-ties and their transference. The study is aimed at providing material for improved differential diagnoses between the neurotic and border-line disturbances.

### B. The Absence of Experimentation in Psycho-analysis. Suggested Use of Experimental Situations Provided by Nature or Fate

The analytic technique as such precludes the setting up of experiments, the only approximation to it being the establishment of the analytic setting itself which acts as an invitation to the patient to re-enact his neurosis under the eyes of the analyst and centred around his person. But this repetition of the neurotic process in the transference represents for the patient a new and complex life-situation and offers no possibility for the artificial isolation of factors.

On the other hand, this embargo on experimentation to which every analyst has resigned himself, can be compensated by the selection for treatment of cases in which either nature, or fate, has caused either the elimination or the exaggeration of one specific either innate or environmental factor. Two projects of the Clinic have been based on this principle.

(i) *An Analytic Study of Children Who are Blind from Birth*
Number of blind children: 8 (ages $2\frac{1}{2}$–12).
Number of analysts and therapists: 6.
Method: Group work in preparation for child-analysis; child analysis.

*Content of study.*—It is a common assumption that visual impressions play an integral part in the individual's early contact with the environment, i.e. in his object-relations and the introjections and identifications built on them, as well as in the mental processes of memory, dream- and fantasy-life. Much additional information about this topic can be gained where the role of imagery is isolated by its total absence from the personality.

Secondarily the same study is aimed at analytic insight into the compensatory processes to be found in the development of totally blind children and into the origin of certain attitudes and qualities of the blind such as the variations in their object-ties, their use of language, their methods of recall, &c.

*Difficulties of study.*—It is important not to overrate the isolation of factors which can be achieved in this manner. The analyst of the blind child has to work through a whole series of complicating secondary factors and disentangle their effect on the child's development from the effects proper of the blindness, quite apart from the frequency of a second, complicating defect. Such secondary factors are: (*a*) the impact on the child of the mother's depression and emotional upheaval consequent on the discovery of the child's defect; (*b*) the severe restriction of mobility which usually occurs in the second year of life to

safeguard the blind child; (*c*) the repeated hospitalizations, surgical interventions with the eyes and traumatic separations from the mother which are the rule with blind children under the management adopted and advocated at present.

(ii) *An Analytic Study of Institutional Children, Orphaned in Early Life*

Number of children and therapists: 6.
Method: Analysis in the latency period, pre-adolescence or adolescence.

*Aim of study.*—This inquiry is aimed at testing the hypothesis that continual absence of mothering from early life onward causes severe abnormality. The deviations of personality development in the absence of a stable mother-relationship emphasize the normal role of the latter by comparison.

Results are obtained especially by studying the transference reactions of these children which reveal (*a*) the primitive character of their object-ties to the adult, (*b*) the substitute ties to individual contemporaries or a group, (*c*) the search for a true mother-relationship in adolescence before the step into adulthood can be made.

(iii) *Further Suggestions for Study*

It is suggested that parallel analytic studies could be undertaken of children who are born deaf, with a view towards establishing the deviations in the development of secondary process-thinking, super-ego formation, and other mental processes normally built on auditory perception.

### C. Comparative Studies Based on Analytic Team-work

*Simultaneous Analysis of Mother and Child for the Purpose of Inquiring into the Interrelation between Neurotic or Psychotic Disorders of Mothers and their Children*

Number of mother-child couples: 8.
Number of analysts and child-therapists: 16.
Method: Adult analysis, child analysis.

Current analytic opinion ascribes almost every abnormality of a child to a latent or manifest abnormality of the mother, an assumption which needs further examination and validation. Detailed demonstration is needed also of the various ways in which the mother's unconscious mental life, her fantasy-activity, her anxieties, her symptoms, &c., reach and affect the child's mental processes. Interrelations of this nature cannot be examined satisfactorily if only one partner of the mother-child couple is analysed, the other partner merely observed and interviewed. The method of choice is the simultaneous analysis of both partners.

*Procedure.*—The analyst of the mother and the analytic therapist of the child communicate weekly the material of their respective patients to a third, co-ordinating analyst for correlation and comparison. In some cases no communication exists between the therapists themselves; in other selected cases such communication is permitted for experimental purposes.

### D. Verification Studies (Comparison of Observational with Analytical Data)

(i) *Comparison of Material Elicited in the Analyses of Older Children with Existing Observational Data Recorded in Their First Two Years of Life*

Number of adolescent children in analysis: 4.
Number of analysts and child-therapists: 4.

When establishing the life history of a patient from his analytic material, every analyst would welcome confirmation of his reconstructions, at least so far as historical and environmental data are concerned. Ordinarily such confirmation from outside depends on chance. To counteract the lack of confrontation of external and internal reality, a longitudinal study has been set up recently in the United States (by Ernst Kris in the Child Study Center, Yale University) to collect all available observational data concerning the development of a given number of infants, to be held for comparison with the result of their analysis in later childhood.

The Hampstead Clinic has similar material at its disposal. In connexion with a study on identical twins, a detailed observational record of a number of infants had been compiled by some of the Clinic workers during their war-work in the Hampstead Nurseries. The present analysis of 4 of these children, now adolescent, offers constructive and revealing material concerning the processes of inner elaboration of external events, distortion of memories by developmental processes, the formation of cover-memories, &c.

For results of this project see the following preliminary report given by Mrs. Dorothy Burlingham (p. 943).

(ii) *Inquiry into the Difficulty of Diagnosis by Comparing the Impressions in the Diagnostic Interviews with the Material Elicited in the Course of the Analysis*

For the details of this project see the following preliminary report given by Dr. L. Frankl (p. 945).

### E. A Study of Child Heroes, Carried Out with a Combination of Methods

The case-material of the Clinic contains predominantly instances of breakdowns, regressions and malfunctions in ego- and super-ego development. In contrast to these neurotic and borderline cases it is of interest to inquire into the opposite phenomenon, i.e. children where qualities such as altruism, social responsibility and capacity for self-sacrifice develop abnormally early or to an abnormally high degree. Although these children are not to be found in clinics, they become conspicuous in society through the performance of heroic acts and are treated as child prodigies in the moral sense. After collecting reports of this kind, a study in three parts has been initiated in the Clinic, of which so far only parts 1 and 2 have been completed.

Part 1 consists of a survey of 30 children (age-range from 4 years to adolescence) who have performed actual *rescue acts*, saving the lives of other children from fire, water or in traffic accidents. They were examined according to parental and family background, intelligence and manifest behaviour, school performance, social adaptation, &c. Their developmental history was investigated so far as this is possible by methods of interviews and questionnaires. Rorschach tests were given.

Part 2 consists of a parallel survey of *rescue fantasies and dreams* collected from 60 cases under analytic treatment at the Clinic. Since this material forms part of the children's analyses, it is possible to group these rescue fantasies according to their unconscious motivation, i.e. to characterize them according to their nature as impulsive manifestations, reaction-formations built up in defence against hostile attitudes and death wishes, identifications with the protective father or mother, &c. None of the children studied in whom rescue fantasies are prominent had carried out actual rescue actions.

Part 3 will consist of the analysis of a small number of selected cases of actual child-heroes This will make it possible to determine the relationship between rescue fantasy and rescue action, to investigate whether the unconscious background of both manifestations is identical and to provide material for a more intensive study of the early development of highly valued social attitudes, such as altruism, capacity for sacrifice, taking responsibility for others at one's own expense, &c.

### F. Pooling of Material—A Methodological Project

As mentioned before, the material of all cases under analytic treatment is made available to all other members of the Clinic by means of weekly and bi-monthly summaries. This makes it common property so far as study and discussion are concerned; for all other purposes, especially for the purpose of publication, it remains the property of the analytic worker who carried out the treatment and should not be used or quoted without permission and acknowledgment.

To make the whole analytical material at the disposal of the Clinic more readily available for use by research workers, a plan has been devised to classify the data, and summarize them in the form of a subject index. For details of this project see the following preliminary report by Dr. C. de Monchaux (p. 946).

**Dr. Ilse Hellman** (London):

*Research on Adolescents in Treatment*

The treatment of adolescents is generally known to present considerable difficulties whatever the nature of the psycho-therapeutic intervention may be. So far the problems of adolescents in psycho-analytical treatment and the specific technical difficulties they present are known to us only from the experience of a small number of individual analysts. We have therefore welcomed the opportunity of studying 15 adolescent patients who are at present in treatment at the Hampstead Clinic as this opens up the possibility of investigating and comparing the material in a way which has not been open to us so far.

*Method of study.*—Miss Freud has referred to the method of pooling, and has described its advantages for psycho-analytic research. This is the method used in our research on adolescents. The 15 child-analysts and child-therapists who are treating the cases in question meet weekly. Each of them in turn brings detailed material from his case illustrating the problem under discussion and comparing his own experience, approach and understanding of the material and technical measures he has taken with those of other members of the group.

*Problems studied.*—As this research started only six months ago it is far too soon to draw conclusions, nor have we attempted to formulate which specific problems we intend to cover. We have found it more profitable to take up problems which we encounter in the material of a number of our patients and see whether these or similar manifestations are present or not in the other cases.

*I. Initial phase.*—Owing to the fact that several cases started treatment at the time when the research project was started, and in view of the well-known difficulties presented by adolescents in the initial phase, it was decided to choose the *first sessions* as the first topic of our investigation. The patients' attitude to their own need for treatment, their anxiety manifested in a great variety of ways, technical measures used in order to reduce their anxiety, the patients' approach to their therapists, first transference manifestations, &c., are some examples of the specific questions studied and compared within the topic of first sessions.

*II. The adolescents' distrust.*—It was found that suspiciousness and distrust play a part in the majority of cases in this group to varying degrees, and that this invariably creates technical problems. For this reason the group decided to choose this as its second topic.

By studying all material containing manifestations of distrust and relating it in each case to the internal and external conditions of each patient as well as comparing common features in different cases, we are working towards a clearer distinction between manifestations of distrust which may be characteristic for this developmental phase versus those built on pathological mechanisms or again largely related to external factors.

Both these topics have implications on the role of the parents in the treatment of adolescents and on the technical problems arising from this; this and many other problems we hope to deal with as our work proceeds.

**Mrs. Dorothy Burlingham** (London):

*Identical-twin Studies*
*Based on the Integration of Observational and Analytical Data*

In the war years when I followed the development of several pairs of identical twins I did so by means of observations through a number of years and gave an account of this in my book on "Twins" (London, 1952). Recently I was able to pursue the investigation of one of these pairs through reports on their treatment in our Clinic by Mr. Arthur Barron. Some other examples brought in for illustration are taken from the treatment of twins undertaken by Miss Agnes Bene, Miss Ivy Bennett and Mr. Oscar Friedmann.

Usually identical twins are considered suitable material for research since they offer the opportunity of distinguishing reliably between inborn factors on the one hand and acquired factors on the other hand. I was naturally involved with this same question. But while observing such manifestations as identical appearance, identical activities and even identical thoughts I found that, although it is true that everything that is inborn is identical, not everything that is identical is inborn. Therefore I tried to answer the question why, in some instances, twins remain similar and in others acquire dissimilarities or regain similarities they had lost.

While taking the identical heredity for granted I began to enquire into the environmental circumstances which either cause or strengthen the identity of twins. I found powerful factors working in this direction in the early mother-relationship.

When one studies a mother's attitude to her twin babies it is easy to see that she does not succeed in treating them as two separate individuals. This is especially noticed in cases when it is difficult to tell them apart and even the mother confuses them. She treats them as a unit, as a group of two, and this has definite repercussions in the twins' development. They fail to develop the feeling that they are individuals in their own right. Neither twin feels special or individual in relationship to the mother.

Then they make the discovery that the only person for whom they are unique is the twin, and this uniqueness produces a special quality in the relationship to each other. At first this relationship to the twin and that to the mother develops side by side, but in time the twin relationship becomes more important and supersedes that to the mother. This becomes especially noticeable at the time of speech development. They create a language that is only understandable to the twin and their first words may be related not to their parents but to emotions felt for the twin.

The mother's failure to relate to each twin separately and to satisfy each child's individual needs has further consequences for the twin relationship. Since identical twins pass through their stages of development simultaneously and require the same emotional response from the mother usually at the same moment, this makes it impossible for her ever

to give either of them undivided love and attention in vital situations, such as being fed, being comforted, being put to sleep. Thus they are rivals from the beginning in their competition for possession of the mother. Since they feel more loved as a unit it brings them together as a pair which makes for identity. But at the same time they are rivals in competition with each other which makes for separateness and dissimilarity. Their jealousies are stronger, so are their death wishes against each other, therefore they feel more guilty. The guilt in its turn intensifies the bond between them and they cling all the closer to each other.

*Change of roles.*—The first personal dissimilarities noticeable in twin infants are due usually to accidental differences in weight and strength. The stronger twin cries more lustily for its food and therefore receives attention first, the weaker one who is less demanding accepts a more passive role. In this way an active and a passive twin result. If an illness occurs and the stronger twin becomes weaker in its turn, the roles are changed and we see the passive twin turning into the aggressive one. Observations such as these made during infancy show that it would be a mistake to take as permanent any dissimilarity which has been established. Any of these can be changed over-night. What is different one day may be similar the next. Parents repeatedly report this fact and the resulting confusion. For example, I know a family with twin boys and followed their development since infancy. The mother often complained of their aggressiveness but sometimes it was one, sometimes the other twin who was blamed for it. When the boys reached adolescence she came to me for help because Jim caused great difficulties at home and although a good pupil in school before, was now threatened with expulsion. Would I see him? When, two weeks later, the boy came to see me, it turned out to be the other twin, not Jim but Ted. Jim was all right now but in his place Ted was behaving so badly in school that he in his turn was faced with expulsion. When later Ted entered treatment he informed his analyst that he had come to the interview with me in his brother's clothes.

*Double birth.*—Twins themselves feel their double birth as a great problem and search suspiciously for dissimilarities as well as similarities in each other. They question their completeness and feel castrated. One boy expressed this problem in the form of questions: "Was he a whole boy or only half a boy? What are twins, half of one or are they two people in their own right?" Mathematics proved impossible for this boy, although he was a good scholar otherwise. His inhibition centred in his inability to solve fractions.

*Position of twins first or second born.*—When twins become aware that one of them has been born before the other, they grasp at this fact as at a tangible and fixed dissimilarity. They brood over it and feel that this situation is of great importance for them. The elder can now feel superior, the younger is forced suddenly to feel inferior.

In one pair known to me the elder considered that he should have been the only one. In another pair, the elder by 20 minutes complained that his mother had not treated him fairly, she had not accorded him his proper place in the family as first-born and quoted from the Bible saying she had deprived him of his birthright.

The second twin also felt deprived and badly treated and considered his brother as the usurper. He complained that another baby was already there when he arrived; he should have been the only one or not born at all.

There seem to be three problems for the first-born:

(1) Was a second child born because he was incomplete, that is, was part of his body left behind, or was there something physically wrong with him?

(2) Was he slow in coming, so that the other child caught up to him?

(3) Or was the twin a dangerous pushing rival who had forced him out too soon?

The second twin's problem may also be a worry that he is incomplete, and that for some reason he has been held back and so came late and then had to fight for his rightful place.

Both twins know of only one solution for their double birth problem, that is to get rid of their twin.

*Opposite tendencies.*—Of course twins have not only their death wishes against each other to contend with, they also have the opposite feelings which counteract these wishes. Guilt for the rivalry as a reaction force has been mentioned already. Most important is the primary identification with the twin, a process which can be observed in all twins from infancy and which continues throughout their whole development. On the basis of this identification, getting rid of the twin would mean getting rid of oneself. Further, there is the erotic pleasure twins get from each other's bodies. Early and continuous contact with each other leads to erotic activities and acts as a seduction.

Recently a pair of 10-year-old twins were brought to the Clinic by their parents because from infancy they had slept intertwined and could not be broken of this habit. One twin remarked in his session, "10,000 hot water bottles would not take the place of my twin nothing can separate him from me".

One of the pairs of twin boys I studied behaved towards each other in a wild and uncontrollable manner, mauling and rolling on each other as puppies do, hitting and punching each other. When analysed as adolescents they were still behaving in exactly the same manner. Only now they resembled tiger cubs, ready to tear each other to pieces. The passionate eroticism of this dangerous play betrayed itself in a rhythmic quality in their hitting and punching.

There was, however, a difference in the behaviour of these two boys which showed in boxing. Both boys loved to box, one only enjoyed boxing without gloves. He liked to feel his bare fists pounding against the body of the other, while the other twin insisted on only boxing with gloves. Fear of his aggression made him count on the padding of the gloves to prevent him from severely injuring his twin.

*Adolescence.*—There are some added features which I can study now following the analysis of the same twins in their adolescence.

In adolescence all children are overwhelmed by their intensified emotions, especially those directed towards their mother, and they try in every possible way to free themselves of this tie. With twins the problem is a double one. To become independent of the twin is as important as the independence of the parent. The twin relationship which has developed since birth into such a close partnership ranks with the mother-relationship. It may even take over many qualities of the mother relationship as well as its intensity and passionateness. Therefore the struggle to break the tie to the twin may take first place in adolescence.

**Dr. L. Frankl** (London):

*Enquiry into the Difficulty of Diagnosis by Comparing the Impressions in the Diagnostic Interviews with the Material Elicited in the Course of the Child's Analysis*

This study aims at assessing the value of initial diagnostic interviews and their limitations and fallacies. This investigation seems important since in Child Guidance Clinics and in reports for Juvenile Courts far-reaching decisions regarding the future of the child are often based on such interviews. The choice of treatment is, of course, also based on interviews and tests. Whereas the reliability and validity of tests have been carefully scrutinized, the value of the initial interviews has not been evaluated in a similar way.

We correlate the observations and the preliminary assessment made at the initial diagnostic interview with the knowledge of the child's personality and psychopathology gained in the course of psychoanalytic treatment.

The first subject of study was the contribution made by the contact with and the observation of the child in the diagnostic situation. For this purpose the detailed records of the complete interview with the child, written immediately afterwards, were carefully studied and viewed from two different aspects:

(1) The means by which the child communicates, that is, the clues he gives us as to his disturbance (appearance, facial expression, movements, verbal communications, play, attitude to psychiatrist, &c.).

(2) The areas for which these communications are relevant, such as the child's affects, the integration of the personality, &c. For instance, we asked ourselves what does the initial contact reveal with regard to the child's social relations? Which aspects of a child's relationship to other people are expressed in his attitude to the interviewer? What could one infer from the children's comments or fantasies about members of the family, friends, teachers, animals?

By comparing these impressions with the findings which emerge in the course of analytic treatment we hope to establish which factors in the interview are the most conclusive ones and to use this knowledge for improving the technique of the diagnostic interview.

Besides studying the initial contact with the child we investigated the differences between the picture of the child's disturbance as conveyed by the parents in their interviews, and the findings of the analysis, regarding the psychopathology of the case. This shows on the one hand the fallacies and limitations of the social history; on the other hand, the usefulness of the interview with the parents.

*Diagnostic Investigation of Current Cases with Special Reference to the Technique of the Diagnostic Interview*

Among the topics studied are measures to allay anxiety, measures to elicit relevant material for the purpose of differential diagnosis, and the use of interventions, precursors to interpretation and interpretation, for the purpose of differential diagnosis.

After the diagnostic interviews, pre-school and school children are being filmed to make the material of the diagnostic investigation available for discussion in a larger group.

*Future Plans*

(1) In order to assess the value of different forms of communication, it would be important not only to see what the initial interview revealed, compared with the later knowledge of the child and his problems, but to study a control group of well-adjusted, so-called normal children and compare their behaviour in a diagnostic interview in the Clinic with that of children who were referred for treatment. This is what we are planning to do.

(2) Further, it will be important to consider what conclusions can be drawn as to the ultimate prognosis from the present psychopathology of the child. In order to investigate this, longitudinal studies are needed. As a pilot study we shall compare records of observations made on children in the Hampstead Nursery when they were quite young with the findings of a follow-up study, and, in a few cases, with the detailed knowledge gained in analytic treatment.

(3) It is hoped that our research into the different problems implied in diagnostic work will not only lead to an improved technique in the diagnostic interview but also contribute to a more satisfactory classification of psychological disorders in childhood than is at present available.

**Dr. C. de Monchaux** (London):

*Pooling of Case Material: a Methodological Project*

Miss Freud has referred briefly to the attempt being made at the Hampstead Clinic to pool psycho-analytic case material for research purposes. I shall outline the procedure we have adopted and indicate some of the problems we have encountered in this work.

All therapists at the Clinic submit weekly and bi-monthly reports on their work in treating patients. These reports are filed in a central office and may be consulted by any staff member. As such reports accumulated, the more formidable became the task of keeping up to date in reading them, and the less often were they consulted. It seemed that a unique opportunity for extensive comparison of psycho-analytic data was being lost, and to remedy this, Mrs. Burlingham put forward the idea of indexing Clinic case material to make it more readily accessible for research and teaching purposes. Under her guidance, a working party has now been engaged on this task for some four years.

Our aim has been to provide a set of subject headings according to which psycho-analytic case material could be classified, so that a research worker interested in, for example, some feature of the psycho-pathology or treatment of bed-wetters, could look up the subject index under the heading "bed-wetting" and find a set of cards indicating in which cases this symptom appeared. If, further, he were interested in consulting the case material of bed-wetters of a certain age group, the subject index would enable him to make this further selection speedily, before he proceeded to draw out the full reports of the appropriate cases from the central case file.

At first sight, the compilation of such an index seemed a straightforward, if laborious, task, but, like the Sorcerer's Apprentice, we found that we had got more than we bargained for, and the indexing of case material has developed into a methodological study in its own right. The reason for this lies not only in the nature of the data we set out to classify, but also in our attempt to proceed empirically from the outset. We were reluctant to use an *a priori* classification, and fit case data to it, considering that such a procedure was likely to lead to serious misclassifications. We recognized that although the therapeutic work of the clinic is guided by common principles of theory and technique, nevertheless there are many sources of individual variation—in the work of different therapists, in their case reporting, in the nature of the case being treated, and so on. To provide a set of categories which would faithfully guide the research worker to the content of case reports, we first studied the way in which therapists themselves classified their case material. As a pilot phase of the project, 50 case reports were indexed by the therapists concerned, in consultation with members of the working party. From this preliminary work, it was possible to derive a set of common categories for use with subsequent cases. By investigating categories used by the therapists themselves, we therefore attempted to reconcile the often conflicting aims of providing for maximum individual initiative and flexibility in report writing and categorization, with the need for a comprehensive classificatory scheme.

The over-determination and many-sidedness of our data led us to adopt a multidimensional scheme of classification. We have made provision for the ordering of any unit of psycho-analytic observation according to the classical groupings of dynamic, structural, developmental and object-relations concepts. For instance, an example of transference behaviour indicating oral dependence may be traced either through its dynamic aspects (oral libidinal and aggressive aims) or through its ego and super-ego aspects, or in its relevance to the course of psychosexual development and social relationships, both within the transference and elsewhere. By a system of cross-referencing, those seeking to find such

an instance of case material may approach it from any of a number of conceptual paths, sign-posted by the index headings.

The therapist is encouraged to order the material of his own case according to those categories which he uses most naturally and readily. His initial categorization can then be extended by cross-referencing. For instance, a therapist may find that he prefers to formulate part of his case material primarily from the point of view of transference significance. This will be reflected in his choice of categories when he classifies his data. The index working party meets him, discusses alternative classifications, and obtains agreement from him as to the cross-referencing of his data. In this way the initiative of the therapist and his own classifying habits are maintained, and yet his case material can be placed within the multidimensional system of the classification as a whole.

The data of psycho-analysis may be described at many different levels, and the same item of observation may be considered in its own right, or as part of a series of progressively more inclusive classes. We have tried to reflect this in our categorization. For example, a symptom may be recorded as such, or as part of a symptom pattern, or from the aspect of its setting in larger patterns such as the complex of object relationships, or in its temporal relation to the course of the treatment, or in relation to phases of psychosexual development.

Like many other systems designed to store information, the case index has had a number of feed-back effects. Its implementation has broadened the scope of report writing, providing a wide frame of reference within which the individual therapist may consider the structure of his cases in comparison with others. Ideas for research have been stimulated by the possibility of scanning a large amount of case material assembled in compact form. Illustrative case material for use in teaching has been made easier to select, and finally, the task of defining concepts for classification purposes has clarified many theoretical issues, and has provided a focus for lively and rewarding theoretical discussion amongst the Clinic staff.

[*June* 10, 1958]

MEETING AT THE ROYAL INFIRMARY, SHEFFIELD[1]

## DISCUSSION ON METHODS OF PSYCHOSOMATIC MEDICINE

**Dr. Denis Leigh** (London):

Psychosomatic medicine is a marginal field of ill-defined boundaries and meaning. Some speak of the psychosomatic approach, that is, the concurrent mental and physical examination of the patient, and would bring all medicine within its purview. In this approach we make an evaluation of a disorder, whatever it may be, from a cirrhotic liver to a broken leg, in terms of the total life setting of the patient. Or again particular attention may be paid to social factors. Halliday, for instance, regards psychosomatic disorders as manifestations of a sick society, a disorganized society and speaks of psycho-social medicine.

I believe that few conditions repay either type of approach. Scientific medicine has advanced far enough for us to have a body of relevant information bearing directly on the cause, outcome and treatment of particular conditions. The handling of the patient and his disease is part of the skill or art of the physician, and it seems presumptuous to invoke a psychosomatic approach. Social and personal factors play some part in disease, but they have shown a precise correlation with only a relatively limited group of disorders.

I propose therefore to regard psychosomatic medicine as a particular branch of medicine, confined to certain disorders, where genetic and constitutional factors are of considerable importance, and where there is a clear and validatable relationship between a mental event and a bodily disorder. This limits the number of psychosomatic disorders considerably. In all these conditions the autonomic nervous system and the neuro-endocrine system are involved, and their study implies a knowledge of these two closely linked systems, and also of the various anatomical and physiological properties of the organs and systems involved, respiratory, gastro-intestinal, vascular, and musculoskeletal.

What are the methods used for studying these disorders? They include all the methods familiar to general medicine or surgery, such as clinical observation, experiment, therapeutic trial. But in these disorders psychiatry enters the field and this is where the difficulty begins. First, psychiatry uses a terminology which has little in common with that of medicine, is still inexact and indeed often obscure. The terms themselves often arouse

[1] This was the first meeting of the Section to be held in a provincial centre and in welcoming Fellows and guests, the President said that he hoped that further meetings would be held in the provinces in future years. After the meeting, Fellows and guests visited the new University Department of Psychiatry at the invitation of the President and were entertained to tea.

strong feelings in the non-psychiatrist; they tend to be bandied about by members of the lay public, and come to be used with no regard for their real meaning. Secondly, psychiatry includes some very specialized fields of knowledge, notably those concerned with mental mechanisms in health and disease. And it is this dynamic psychiatry, as it is called, that presents the gravest difficulties to the non-psychiatrist, for it involves a special knowledge of some particular theory of mental functioning and the mastery of a special technique whereby information is obtained from the patient.

Thirdly, there is the special field of psychology—concerned with the measurement of certain aspects of mental function, such as intelligence, dexterity, verbal facility and with the normal mental functioning.

Psychosomatic medicine therefore demands team work, the physician, the psychiatrist, and the physiologist each bringing his own particular methodology and technique to the problem in hand.

**Dr. Joseph Sandler** (The Tavistock Clinic, London):

*The Use of the Tavistock Self-assessment Inventory in Psychosomatic Research*

With the entry of the Tavistock Clinic into the Health Service, a programme of research was evolved in the Adult Department, to help meet the need for objective personality assessment, with special reference to the factors involved in psychoneurotic and psychosomatic illness.

Following an extensive examination of existing psychological instruments, a special inventory was developed as part of the research programme (Sandler, 1954). The inventory contains a large number of statements made by patients about themselves in the clinical interview situation, and was based on extensive collaborative work between psychologists and psychiatrists at the Clinic.[1] It is a unique instrument, both in the content of its items and in the fact that it is applied in a special setting in which the relevance of the task to the patient's problems and treatment is explained.

The value of the test lies in part in the possibility of treating the results statistically, and a number of investigations have been reported, in which the statistical and psychological approaches are integrated (Sandler and Pollock, 1954; Kanter and Sandler, 1955; Sandler and Rakoff, 1955; Dixon *et al.*, 1957; Hazari, 1957; Sandler *et al.*, 1958; Taçon, 1958; Bishop, 1958; Sandler and Hazari, 1959). Some of these investigations refer to psychosomatic phenomena, in particular to the relation between "functional dyspepsia" and duodenal ulcer. A significant correlation was found between the symptoms of "functional dyspepsia" and multiple specific phobic anxieties. These were found to be present in marked degree in neurotics with dyspepsia, in out-patients with "functional dyspepsia" and in those with duodenal ulcer,[2] and relatively absent in neurotics and normal controls without dyspepsia. The personality profiles of patients with duodenal ulcer and those labelled "functional dyspepsia" were almost identical, emphasizing the underlying similarity between the two groups. On the basis of the statistical ordering of the data, the hypothesis was put forward that patients who develop dyspepsia are those who are driven (by ambition, conscience, nagging wives, &c.) to enter those situations and to perform those tasks which really frighten them. Preliminary findings on the relation between gastro-intestinal upset and school phobia in school children support this view.

A short description was also given of a recent study, using the inventory, into the classification of neurotic psychosomatic symptoms. Four groups of symptoms were isolated (a "general fatigue" group, a "visceral" group, a "voluntary" or "musculo-skeletal" group and an "orifice" group). This grouping has statistically significant psychological correlates which confirm and extend findings based on clinical impression alone.

REFERENCES

Bishop, J. (1958) An Investigation into the "Schizoid" Character. Ph.D. thesis, London.
Dixon, J. J., de Monchaux, C., and Sandler, J. (1957) *Brit. J. med. Psychol.*, **30**, 34, 107.
Hazari, A. (1957) An Investigation into Obsessional Anxieties. Ph.D. thesis, London.
Kanter, V. B., and Sandler, J. (1955) *Brit. J. med. Psychol.*, **28**, 157.
Sandler, J. (1954) *Brit. J. med. Psychol.*, **27**, 142.
——, de Monchaux, C., and Dixon, J. J. (1958) *Brit. J. med. Psychol.*, **31**, 24.
——, and Hazari, A. (1959) *Brit. J. med. Psychol.* (in press).
——, and Pollock, A. B. (1954) *Brit. J. med. Psychol.*, **27**, 146, 235, 241.
——, and Rakoff, V. (1955) *World Sci. Rev.*, November, p. 25.
Taçon, S. (1958) An Investigation into the Classification of Psychosomatic Symptoms. Ph.D. thesis, London.

[1]Under the general supervision of Dr. J. D. Sutherland, Medical Director of the Clinic.
[2]Provided by Dr. Avery Jones and his Unit at the Central Middlesex Hospital.

**Dr. Max Hamilton** (Leeds):

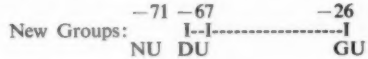
*The "Duodenal Ulcer Personality"—a Psychometric Approach*

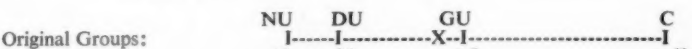
In this symposium on methods of research on problems in psychosomatics, the present paper is intended to illustrate the use of psychometric methods, applied to the problem of the so-called duodenal ulcer personality.

Physicians have repeatedly drawn attention to the special characteristics of personality of patients suffering from duodenal ulcer. There is now an extensive literature on the subject, with much disagreement between authors, but two important problems can be distinguished: there is general agreement that these patients tend to have anxious and tense personalities, with disagreement whether they are neurotic or not; it is asserted that they have an obsessional type of personality, although this has sometimes been questioned.

A previous paper (Hamilton, 1950) described the results from the use of a special inventory given to four matched groups of patients, suffering from duodenal ulcer (DU), gastric ulcer (GU), non-ulcer dyspepsia (NU), and a control series (C) of patients in hospital. The results were analysed by the method of Rao multiple discriminant functions. This gave three functions (vectors) which differentiated between the four groups, but only one was statistically significant. This means that the four groups of patients can be described as having more or less of a single quality, consisting of a particular combination of traits, and this adequately describes the differences between the groups. The conclusion was that there is no specific type of duodenal ulcer personality. The combination of traits consists chiefly of anxiety, dependence and guilt feelings, and was tentatively labelled as anxiety neurosis.

The present paper describes attempts to confirm these conclusions. The inventory was administered to new groups of patients, and the mean scores on the discriminant vector calculated. They are given below; for convenience, the scores of the original groups are also shown.




It will be seen that there is a shift to the left of all the scores, but the relative position of the groups is the same. It is considered that the results are reasonably in agreement with the original findings.

To test whether the combination of traits could appropriately be called anxiety neurosis, the inventory was given to a group of patients suffering from anxiety neurosis. They had a mean score of −110, i.e. they were much beyond even the non-ulcer dyspeptics, and the difference is highly significant. This finding is in agreement with the hypothesis.

The most interesting point in the original results is the absence of traits characteristic of the obsessional personality. Two explanations are possible: that duodenal ulcer patients are not characterized by obsessional personality traits, or alternatively, the inventory is incapable of detecting such traits. The latter is quite likely, since inventories are by no means the best method of investigating personality. To test this, the inventory was given to a number of patients who had markedly obsessional personalities as judged by psychiatric anamnesis. It was found that their mean score on the trait of perfectionism was 3 standard deviations greater than the original control series, and over two S.D.s from the mean of all patients. There can be no doubt therefore that the inventory can detect perfectionism, the characteristic trait of the obsessional personality. It may be added that duodenal ulcer patients have their fair share of obsessional personalities, but this type of personality is not uncommon in the general population, and it does not distinguish this type of patient from others.

REFERENCE

HAMILTON, M. (1950) *Brit. J. med. Psychol.*, **23**, 182.

**Dr. R. H. Gosling** (London):

Psychosomatic disorders may be studied by a number of methods. One that has a long and respected history in the medical sciences is the epidemiological. In this, the incidence of a particular disorder is surveyed in a variety of circumstances so that a significant association, positive or negative, may be demonstrated between the disorder and a particular

circumstance. In this approach there is always an implied hypothesis, i.e. that certain circumstances in preference to others are related to the disorder. It may be a rather general hypothesis; for example, that the disposition to various mental disorders is related to the incidence of peptic ulcers. On the other hand, it may be a much more precise one; for instance, that an individual who adapts to stress by relinquishing a large part of his higher mental organization will tend not to show other so-called stress disorders: which hypothesis might lead us to expect that amongst schizophrenics the incidence of peptic ulcer would be low. Such an epidemiological survey has indeed been carried out in which the incidence of peptic ulcer was studied in a population of psychiatric in-patients.

A problem always besetting this method of study is the difficulty of getting a sample for study that is representative of the population at risk, and however much care is taken one cannot be certain that some biased sampling has not taken place. For instance, the incidence of peptic ulcer is known to be higher in older people than in younger; the low incidence of ulcer found in a sample of schizophrenics might then be due to the inclusion in it of a disproportionately large number of young individuals. To overcome such a bias in the sampling procedure, a correction must be made for the age composition of the samples being compared. In fact the low incidence of ulcer amongst schizophrenics was found to hold even after correction for the influence of age. But there always remains the possibility that some unsuspected variables are at work. Some can be discredited by inspection of the experimental conditions, though a more definitive experiment would be required to clinch the matter. For example, it might be suggested that the low incidence of ulcer amongst schizophrenics is due to their protection from the stress of daily life by their being in institutions. In the sample studied, this does not appear to have been an important factor, as the vast majority of patients had not been hospitalized for more than a few months.

When a considerable number of psychiatric categories are investigated for a high or low incidence of ulcer there is a substantial possibility of a chance association, particularly when the samples are small. For example, amongst the few patients with asthma who had been admitted to the psychiatric hospital for psychotherapy for this condition, it was found that a surprisingly large proportion had a history of peptic ulcer. Little reliance could be put on this finding, however, until it came to light that the same tendency was shown in a second sample of asthmatics, this one consisting of patients attending a near-by general hospital. The method can also throw light on some of the many assertions having more the status of clinical aphorisms than formal hypotheses, such as that psychotics rarely get ulcers. It was confirmed that in our sample of psychotics there were slightly fewer ulcers than in the rest of the population, but it further came to light that this was due almost entirely to the inclusion of so many schizophrenics amongst whom ulcer was decidedly rare.

Further findings in this survey were that ulcer was significantly more frequent amongst alcoholics and amongst patients with reactive depressions; but as the possibility always remains that each one of these correlations may be due to an unsuspected bias in the sampling, each requires confirmation either from a second survey of a similar population, or from a study using a quite different approach.

# Section of Odontology

President—G. T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S., L.R.C.P.

[*March* 24, 1958]

## Some Abnormalities in the Nerve Supply of the Oral Mucosa

By E. A. MARSLAND, Ph.D., B.D.S., L.D.S.Eng., and
E. C. FOX, M.D., L.D.S.Edin.

*Departments of Dental Pathology and Periodontology, School of Dental Surgery, University of Birmingham*

### *Introduction*

IN view of the numerous painful conditions which occur in the mouth and the problems many of these present to the dental profession, it is surprising that the possibility of variations in the distribution of peripheral nerves has received so little attention. Stones (1956) reviewed the ætiological factors in facial pain but comprehensive as this account was, it gave only brief consideration to the possibility of local abnormalities in the peripheral nerve supply.

Attention has been paid in the past to the nerve supply of the tongue (Aprile *et al.*, 1955; Gairns, 1953*a*), the palate (Gairns, 1953*b*), the lip (Hagen *et al.*, 1953), and the periodontal membrane (Bradlaw, 1939; Held and Baud, 1955; Lewinsky and Stewart, 1936; Rapp *et al.*, 1957). The innervation of the normal gingiva has also been investigated (Bradlaw, 1936, 1939; Gairns and Aitchison, 1950; Rapp *et al.*, 1957; Stewart and Lewinsky, 1939). Encapsulated and unencapsulated endings have been described which are similar to those reported in the skin by Weddell (1941), Winkelmann (1955) and Woollard (1936). Fig. 1, taken from the paper by Gairns and Aitchison, illustrates diagrammatically their conclusions on the innervation of the normal gingiva.

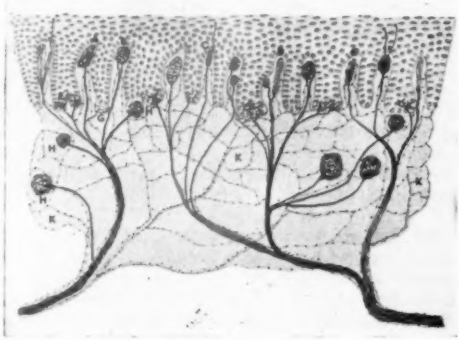


FIG. 1.—Diagram of a section through the human gum to show the types of nerves and nerve-endings and their distribution. A, Large "whorl" type ending. B, Unencapsulated end bulb. C, Ending with "ultra-terminal" fibre entering the epithelium. D, Long open mesh type of ending. E, Encapsulated corpuscle—Meissner. F, Intra-epithelial endings. G, Subepithelial plexus of nerves. H, Typical Krause corpuscles at various levels of the dermis. K, The sympathetic ground plexus.

*Reproduced from Gairns and Aitchison* (1950) *by kind permission.*

Little is known about the reaction of these local nerve elements to extraction of the teeth. Bradlaw (1936) found evidence of regeneration of severed apical nerves after extraction of teeth. He stated that "it is known that a response to stimuli is given by regenerated nerve fibrils with abnormal ease and the sensation thus elicited is unusual in character and spreads widely" and suggested this might explain neuralgia following multiple extractions.

For many years patients who are unable to tolerate dentures because of constant pain and discomfort along the alveolar ridge have presented a problem. In particular the lower anterior region causes trouble and the wearing of a lower denture may be impossible. In many instances the cause of the soreness cannot be found and the treatment in consequence is unsatisfactory. Saunsbury (1954) pointed out that the familiar methods of treatment for such a condition are surgery, soft lining inserts, and bold relief of the area on the master model, He found that, of the patients who underwent partial alveolectomy and smoothing of the alveolar crest, slightly more than half had the same pain a year after the surgery. Although Saunsbury dealt specifically with pain and discomfort in the lower anterior region the problem is encountered in other parts of the alveolar ridge, both upper and lower, though with less frequency.

During the last three years 82 of these cases have been investigated at Birmingham. All the patients complained of a severe persistent neuralgic type of pain which was often likened to continuous toothache. The patients could be divided into two groups. In the first group, comprising 72 patients, the pain and discomfort appeared shortly after the extraction of teeth and became more distressing when dentures were fitted. A second group (10 patients) complained of pain and discomfort only after they had worn full upper and lower dentures for many years. Generally the pain in this second group was not relieved by leaving out the denture though in some patients the intensity of the pain diminished, but in no case did it completely disappear. Routine prosthetic procedures such as the making of new dentures, provision of relief, or the use of soft base materials were of little value for, at best, they gave only temporary alleviation.

Clinical examination of the patients showed that, in areas where pain was present, the mucosa covering the alveolar ridge had a slightly whitened appearance. Subsequent histological examination of these areas showed the epithelium to be hyperkeratotic. Application of light pressure with a blunt probe to these areas showed that they did not react to this stimulus in a uniform manner; parts of the zone of hyperkeratosis were no more sensitive to pressure than the normal alveolar mucosa in symptom-free areas of the mouth. In other parts, however, there were spots which were hypersensitive to pressure and the mere touching of these "trigger spots" was enough to produce quite severe paroxysms of pain. These hypersensitive spots could be mapped out very accurately with a blunt probe and they were found to be about 3 mm. in diameter. Their distribution was not regular but it was usual to find several in each painful hyperkeratotic area.

Table I shows the location of these lesions in 82 patients examined by one of us (E. C. F.). In our cases the problem was not confined to the lower anterior region and 22 patients had pain in both jaws. Table II shows the sex and age incidence.

TABLE I.—LOCATION OF PAIN AND SORENESS IN 82 PATIENTS

| | Region | | | Total |
|---|---|---|---|---|
| | 4–4 | 6–6 | 6–8 | |
| Maxilla .. | 9 | 14 | 9 | 32 |
| Mandible .. | 29 | 32 | 10 | 71 |

TABLE II.—SEX AND AGE INCIDENCE

| | Years | | | | | Total |
|---|---|---|---|---|---|---|
| | 27–30 | 30–40 | 40–50 | 50–60 | 60–75 | |
| Male .. | 1 | 3 | 9 | 4 | 2 | 19 |
| Female | 2 | 9 | 17 | 22 | 13 | 63 |

Radiographic examination of the bone beneath these sore areas showed delayed healing of sockets and lack of cortical bone along the crest of the ridge. Vertically arranged calcified spicules were present along the crest. When the lower anterior region was involved prominent nutrient canals were almost invariably seen.

As a result of the clinical finding that hypersensitive "trigger spots" were present in these patients it was decided to investigate these areas more fully with particular reference to their nerve supply.

It is clear that any investigation into possible abnormalities of the local innervation of the soft tissues of the oral cavity must be based upon a knowledge of the normal distribution of nerves in those tissues. A careful search through the literature has, however, so far failed to produce any reports dealing with the innervation of the mucous membrane covering the edentulous ridge. At the outset of this investigation, therefore, we found ourselves seriously hampered by lack of knowledge on the innervation of the soft tissues of the normal edentulous mouth. In this context "normal" is understood to mean an edentulous mouth showing no indication of disease and in which there is no pain or discomfort, with or without dentures.

The present investigation has, therefore, proceeded along two lines. First, a limited study of the innervation of alveolar mucosa from normal mouths was undertaken. Second, a more detailed examination was carried out on biopsies taken from edentulous patients complaining of severe pain and discomfort arising from the alveolar ridge. In these patients the whole area showing hyperkeratosis was removed but the biopsy was trimmed in such a way that the sections obtained were through "trigger spots". Where possible, the soft tissue was removed together with the underlying bone so that the mucosa could be studied in its correct relationship to the hard tissue.

Three techniques were used for staining nerves. Thin serial sections were stained by a modification of the Ungewitter silver nitrate technique (Rowles and Brain, 1958). Frozen sections were prepared and stained according to the modified Bielschowsky-Gros method used by Gairns and Aitchison (1950). The third method, which does not appear to have been used previously on oral mucosa, was the intravital injection of methylene-blue followed by excision of the injected tissue and the preparation of frozen sections.

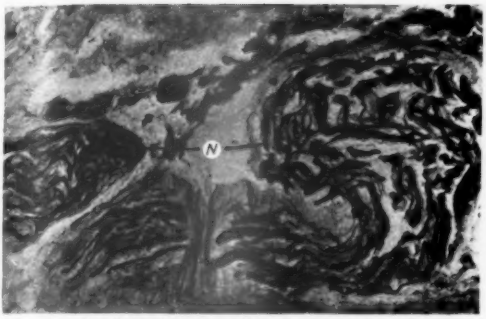



FIG. 2.—An irregular nerve bundle (N) in the submucosa of a normal edentulous alveolar ridge. Stained by the modified Ungewitter's silver nitrate method. × 300.

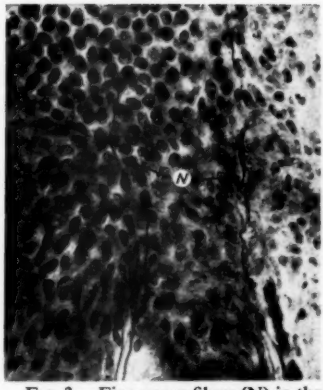



FIG. 3.—Fine nerve fibres (N) in the deeper cell layers of the epithelium covering the alveolar ridge in a normal edentulous mouth. Frozen section stained by the modified Bielschowsky-Gros method. × 350.



FIG. 4.—Part of the mucosa of the alveolar ridge of a normal edentulous mouth showing a coil type of nerve ending in a connective tissue papilla. Frozen section stained by the modified Bielschowsky-Gros method. × 250.

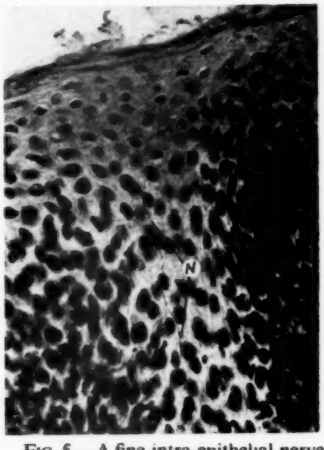



FIG. 5.—A fine intra-epithelial nerve fibre (N) passing up to the surface layers of the epithelium. Frozen section stained by the modified Bielschowsky-Gros method. × 250.

*The Innervation of Normal Edentulous Mucosa*

So far it has been possible to investigate only comparatively few areas of healthy alveolar mucosa from edentulous patients but the results obtained indicate that changes take place in the peripheral innervation as a result of extraction of the teeth. In the mucosa covering the edentulous alveolar ridge a plexus of nerves could be seen in the deeper parts of the subepithelial connective tissue. This plexus was formed of bundles of myelinated fibres which followed a general course parallel to the surface. Some of the fibre bundles were large, and their arrangement was irregular when compared with that described in the normal gingiva around a standing tooth. Frequently the individual fibre bundles were irregular in shape and sometimes they had the appearance of a small form of amputation neuroma rather than an orderly collection of nerve fibres (Fig. 2). From this deep plexus myelinated nerves passed towards the surface to form a fine subepithelial plexus immediately around the basal layer of the epithelium. The fibres of this superficial plexus often ran




FIG. 6.

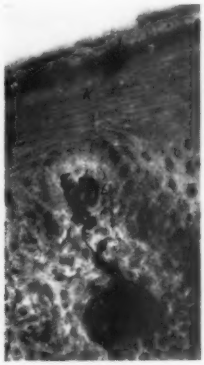


FIG. 7.



FIG. 8.

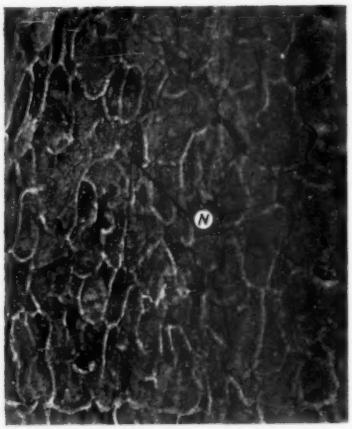



FIG. 9.

FIG. 6.—Large irregular nerve bundles (N) in close relationship to the rough edge of the bone (B). Section through a "trigger spot" stained by the modified Ungewitter's silver nitrate method. × 70.

FIG. 7.—A close coil type of nerve ending (C) towards the tip of a connective tissue papilla in the area of a "trigger spot". The branch (B) ends in a loose coil (L) immediately beneath the surface layer of keratin (K). Frozen section stained by the modified Bielschowsky-Gros method. × 250.

FIG. 8.—A flat disc-like nerve ending at the tip of a connective tissue papilla in a hypersensitive "trigger spot". The nerve ending lies immediately beneath the layer of flattened surface cells. Stained by the modified Ungewitter's silver nitrate method. × 360.

FIG. 9.—"Ultra-terminal" intra-epithelial nerve fibres (N). Section through a "trigger spot" stained by the modified Ungewitter's silver nitrate method. × 360.

parallel to the basement membrane for considerable distances and gave off fine branches which ran into the epithelium and ramified around the cells of the deeper layers. A considerable number of fine nerve fibrils were seen in the deeper cell layers of the epithelium (Fig. 3). Careful examination of serial sections showed that these fine intra-epithelial fibres did not penetrate far and it was not possible to trace a fibril of this type running up to the surface layers of cells.

Other branches from the deep plexus did not contribute to this sub-epithelial plexus but passed straight into the papillæ of the connective tissue where they ended in a variety of ways. It is impossible here to describe adequately the diverse types of ending seen in the papillæ for they differed in form as much as the many endings which have been described in the normal gingiva. Close and loose coils composed of thick and thin fibres were seen most commonly (Fig. 4). Many variations in the morphology of these coils were seen but it is possible that they were modifications of the same basic type of unencapsulated nerve ending.

Encapsulated endings appeared to occur only rarely in the normal mucosa covering the alveolar ridge. They were not present in anything like the numbers that have been reported in the normal gingivæ. Krause corpuscles were seen in the deeper connective tissue but in our experience endings of the Meissner type were rare.

The most striking difference between the innervation of the gingiva and mucosa of the edentulous alveolar ridge was the paucity of long intra-epithelial fibres in the latter. The majority of workers have expressed the opinion that fine endings are present in the epithelium of the gingivæ (Aprile *et al.*, 1955; Bernick, 1957; Bradlaw, 1939; Kadanoff,

1928; Kokobun, 1929; Stewart and Lewinsky, 1937) but others (Held and Baud, 1955; Rapp *et al.*, 1957) were unable to satisfy themselves that these fine fibres exist. Gairns and Aitchison (1950) have described endings in the connective tissue papillæ which give off "ultra-terminal" fibres which run in a straight course through the epithelium to the outer layer of cells. These fine fibrils are considered to be unique to the gingivæ (Gairns and Aitchison, 1950) and the mucosa of the hard palate (Gairns, 1953*b*). Such fine terminal fibrils were seen in the epithelium of the normal edentulous jaw but they occurred only occasionally. They were demonstrated with all three staining methods used but so infrequently as to suggest strongly that some reduction in the incidence of these endings generally takes place after extraction of teeth. Where they do occur they may branch, particularly near their termination, and usually end as fine points (Fig. 5).

The results of this phase of the investigation show that in some respects the innervation of normal mucosa from the edentulous alveolar ridge differs from that of the normal gingiva. The evidence presented indicates that, although some regeneration of nerves severed during extraction of teeth takes place, the resultant distribution of the nerve elements in the mucosa of the edentulous ridge is less orderly. In addition the soft tissues covering the alveolar ridge do not appear to be as profusely innervated as the normal gingiva.

*Histological Examination of Biopsies from Patients Complaining of Pain and Discomfort*

In these patients the most striking additional variations in the local nerve supply of the alveolar mucosa were seen in the "trigger spots" within the hyperkeratotic areas. Before these are described in more detail attention must be drawn to some features seen by routine staining of sections of the excised tissue. The surface epithelium generally showed irregular thickening with, in many cases, a moderate degree of hyperkeratosis. In other patients, the surface cells of the epithelium were parakeratotic. A slight degree of infiltration with chronic inflammatory cells, predominantly lymphocytes, was usually seen in the connective tissue immediately beneath the epithelium. Careful orientation of the biopsies so that the plane of section passed through known "trigger spots" showed that the papillæ of the connective tissue in these areas penetrated deeply into the epithelium. Often the tips of groups of papillæ were covered by only a few flattened surface cells or a layer of keratin.

The pattern of innervation in these "trigger spots" showed many variations in the different biopsies examined. Areas hypersensitive to light pressure with a blunt probe were always found to contain a greater amount of nerve tissue than mucosa giving no such abnormal response. Both the connective tissue and the epithelium shared this increased distribution of nerves.

In the connective tissue at a level below the papillæ, localized groups of irregularly arranged nerve bundles were present. Serial sections were necessary to obtain a complete picture of the disorderly nature of these nerve masses and the individual bundles were found to have a complex intertwining arrangement. Between the bundles of nerve tissue there were loosely arranged collagen fibres. The confused mass of myelinated nerves and collagen so formed was a consistent finding in "trigger spots" although it showed considerable variation in both size and arrangement.

In those cases where it was possible to remove the hypersensitive part of the mucosa together with the underlying bone, another interesting distribution of nerves was seen. Histologically the crest of the alveolar ridge was rarely composed of smooth cortical bone but was uneven with frequent sharp spicules of cancellous bone. Large irregular nerve bundles were seen in close proximity to the rough bone (Fig. 6). The course of these myelinated nerves was again unusual and they formed knot-like masses which frequently lay right against a sharp edge of the bone. In addition to these convoluted nerve bundles, smaller fibres and even individual fibrils were seen running in close relationship to the sharp bony spicules.

Within the papillæ of the connective tissue a wide variety of nerve endings was seen. In general, these endings were similar in morphology to those seen in the same site in normal mucosa but, in the "trigger spots", many of them were situated much closer to the surface of the epithelium (Figs. 7 and 8). This was due to the abnormal arrangement of the connective tissue and epithelium in these areas. In this superficial position, nerve endings are extremely susceptible to injury and are likely to undergo deformation beneath even the best fitting denture.

Another abnormal distribution of the intrapapillary nerves appeared to be unique to the "trigger spots" and was not seen in any of the specimens of normal aveolar mucosa. The papillæ involved were rather larger than is usual and large numbers of nerve fibres ramified throughout the connective tissue. As they passed towards the surface the nerves branched repeatedly to form a network with no definite end-bulbs.

The last abnormality in the distribution of nerve tissue in the "trigger spots" was a

remarkable increase in the number of "ultra-terminal" fibrils in the epithelium. Whereas in the normal mucosa covering the alveolar ridge these fine terminal fibrils occurred only sparingly, in the "trigger spots" they were much more widely distributed and it was often possible to demonstrate four or five in one field under high magnification (Fig. 9). Continuous focusing on different planes of frozen sections or the preparation of thinner sections showed that ultra-terminal fibrils ended just below the keratin layer of the epithelium.

*Treatment*

In the series of cases upon which this report is based we have found that surgical treatment is essential and should be directed towards two ends. First, the "trigger spots" and their abnormal nerve tissue must be removed. These hypersensitive spots should be carefully mapped out with a blunt probe and the precise location and removal of these areas are essential if treatment is to be successful. Second, the underlying bone must be smoothed down and shaped to form an even base for the denture. Particular attention should be paid to producing a functional ridge from the prosthetic point of view and the reduction in the height of the ridge is kept to a minimum. Alveoloplasty is the procedure of choice; alveolectomy is not advocated.

The initial incision is made on the labial or buccal aspect of the alveolus and slightly below the ridge. The soft tissue is reflected from the ridge and the exposed bone made smooth with rongeurs and bone files. The hyperkeratinized strip of mucosa containing the "trigger spots" is then excised and the wound closed by interrupted sutures. Slight freeing of the mucosa on the labial or buccal aspect of the ridge may be necessary to allow satisfactory closure of the incision. This treatment was completely successful in 71 patients. New dentures were fitted and some of these patients have now been followed up for three years without recurrence of the pain and discomfort. Of the remaining 11 patients, 5 showed considerable improvement; the "trigger spots" did not reappear and there were no longer spontaneous attacks of pain but unfortunately dentures could be tolerated for only limited periods of time.

*Conclusions*

While further work is needed before a full evaluation of the effects of extraction of teeth on the local innervation can be given, the results of this investigation indicate that abnormalities in the distribution of nerves may be present in the mucosa of the edentulous mouth. The fact that a marked increase in the amount of nerve tissue may be present in areas causing pain and discomfort beneath dentures appears to be significant. It is known that the usual stimuli which evoke pain in skin or mucous membranes are mechanical deformation of the surface and its contained endings (Bishop, 1949) or their exposure to chemical agents released from neighbouring damaged cells. Both factors may be operative in the case of pain beneath a denture but in view of the very superficial position of the abnormal nerve bundles and endings shown by the results of this investigation, consideration must obviously be given to the mechanical effect of the denture. It is particularly significant that operative removal of the "trigger spots" relieves the pain.

*Acknowledgments.*—We wish to record our appreciation of the help given by Mr. T. C. Graty of the Department of Prosthetics, University of Birmingham. We also wish to thank Mr. E. B. Brain for his help and advice and Miss J. C. Underhill of the Department of Dental Pathology for her painstaking technical assistance.

REFERENCES

APRILE, E. C., ANDERSEN, D., and TESORIERI, A. (1955) Les Parodontopathies. Venice.
BERNICK, S. (1957) *Oral Surg.*, **10,** 323.
BISHOP, G. H. (1949) *J. Neurophysiol.*, **12,** 51.
BRADLAW, R. (1936) *Proc. R. Soc. Med.*, **29,** 507; (1939) *Proc. R. Soc. Med.*, **32,** 1040.
GAIRNS, F. W. (1953*a*) *J. Physiol.*, **121,** 33; (1953*b*) *J. Physiol.*, **123,** 26.
——, and AITCHISON, J. (1950) *Dent. Rec.*, **70,** 180.
HAGEN, E., KNOCHE, H., SINCLAIR, D. C., and WEDDELL, G. (1953) *Proc. roy. Soc.* Ser. B, **141,** 279.
HELD, A. J., and BAUD, C. A. (1955) *Oral. Surg.*, **8,** 1262.
KADANOFF, D. (1928) *Z. Zellforsch.*, **6,** 637.
KOKOBUN, S. (1929) *Dtsch. Mschr. Zahnheilk.*, **47,** 881.
LEWINSKY, W., and STEWART, D. (1936) *J. Anat., Lond.*, **71,** 98, 232.
RAPP, R., KIRSTINE, W. D., and AVERY, J. K. (1957) *J. Canad. dent. Ass.*, **23,** 637.
ROWLES, S. R., and BRAIN, E. B. (1958) To be published.
SAUNSBURY, P. (1954) *Brit. dent. J.*, **97,** 173.
STEWART, D., and LEWINSKY, W. (1937) *J. Anat., Lond.*, **72,** 531.
——, —— (1939) *Proc. R. Soc. Med.*, **32,** 1054.
STONES, H. H. (1956) *Proc. R. Soc. Med.*, **49,** 39.
WEDDELL, G. (1941) *J. Anat., Lond.*, **75,** 346, 441.
WINKELMANN, R. K. (1955) *Arch. Derm. Syph., Chicago*, **71,** 373.
WOOLLARD, H. H. (1936) *J. Anat., Lond.*, **71,** 54.

# Section of Pædiatrics

President—A. Doyne Bell, M.A., D.M., F.R.C.P.

[*April* 18, 1958]

## Bladder Neck Obstruction

By D. Innes Williams, F.R.C.S.
*London*

For many years it has been customary to believe that all sphincter muscles in the body are liable to a curious and unexplained disorder of function unassociated with any histological change, leading to obstruction of flow through the orifice which they are intended to guard. "Marion's disease" has been regarded as such a functional disorder of the internal sphincter of the bladder, but doubt has recently been thrown upon this idea and this paper is concerned with the clinical problem of so-called bladder neck obstruction in the light of recent advances which have been made by Bodian (1957) in our knowledge of the pathology of the congenital lower urinary tract obstruction.

Any diagnosis of obstruction by a functional disorder of a sphincter is essentially a diagnosis by exclusion: the presence of obstruction is easily recognized by the proximal dilatation and the muscular hypertrophy; no organic cause can be found and a functional one must therefore be postulated. In the case of the bladder neck, hypertrophy of the internal sphincter itself was recognized and believed to be the primary disorder as in hypertrophic pyloric stenosis, but examination of cases of congenital urethral valves and other distal obstructions shows that hypertrophy of the muscle of the internal sphincter always accompanies hypertrophy of the whole detrusor coat, of which it is but a part, and the same is true of hypertrophy due to prostatic obstruction in later life.

The process of diagnosis by exclusion naturally leads to variations in the criteria of diagnosis from one centre to another and it is obvious that in some children's clinics bladder neck obstruction is a common and frequently a mild disorder affecting boys and girls of all ages, whereas in others it is a rare but severe disorder causing renal failure in early life. Miller and his colleagues (Miller, 1956) found that nearly half of all their persistent enuretics suffered from bladder neck obstruction, whereas a most thorough investigation of over 1,100 cases of lower urinary tract disorders in the Karolinska Hospital in Stockholm revealed only 6 cases (Kjellberg *et al.*, 1957). Many such glaring discrepancies could be cited from the world literature and it is clear that bladder neck obstruction means different things to different people. It will continue to do so until an indisputable pathology is established.

Looking into my own practice I can readily understand the confusion in diagnosis; there are many cases which I find hard to fit into precise categories and I believe there are several distinct disorders hiding under the diagnosis of bladder neck obstruction: in some it does not appear that the bladder neck is the real site of the obstruction. The disease Bodian has named urethral fibro-elastosis is the first example of this point. The characteristic finding in this disease, which only became obvious when whole post-mortem specimens were examined, is a sleeve of fibrous and elastic tissue enveloping the whole posterior urethra, most concentrated in the region of the verumontanum. The disorder is probably connected with the developing prostate, since the fibro-elastosis replaces the normal glandular and muscular tissue. It is postulated that this sleeve prevents the normal distension of the urethra which should occur during micturition; it therefore constitutes a functional obstruction and leads to detrusor hypertrophy. The bladder neck hypertrophy is part of the reaction of the detrusor, not the cause of the obstruction.

So far all the proved cases have been male and mostly in their infant years, the bladder and upper urinary tract changes have closely resembled those found in congenital urethral valves with a thick bladder wall, heavy trabeculation and sometimes sacculation, together with gross ureteric dilatation and hydronephrosis. Clinically they have been cases of chronic retention of urine, presenting with signs of renal failure, with overflow incontinence of urine or with persistent pyuria. The presence of urinary obstruction is easily recognized, bladder neck hypertrophy may be evident but the urethra itself appears normal or almost normal to radiological and endoscopic examination.

Treatment in the past has been by bladder neck resection, either through the open bladder or transurethrally, but it has always been difficult to restore normal micturition in this group of severely obstructed infants: in several cases I have had to resort to repeated dilatations and fulgurations to get them going, while in later childhood when they are active and

seemingly cured, it is found that they suffer some stress incontinence of urine, due to apparent sphincter weakness. It is now clear that a wedge resection of the bladder neck will remove only a part of the true obstructing lesion, the fibro-elastosis sleeve, and the difficulty of restoring normal micturition is easily explained, while the interference with the whole sphincteric mechanism consequent upon the presence of the fibro-elastosis accounts for the later stress incontinence. During the last two years I have performed a Y–V plasty on the anterior urethrovesical junction as an alternative to bladder neck resection: this brings down a tongue of healthy bladder muscle to widen the posterior urethra, and at the same time allows an opportunity to take a biopsy of the urethral wall which may confirm or deny the presence of fibro-elastosis. Although this operation is sometimes very tiresome to perform, I have found the results more satisfactory than those of the earlier procedure.

Here we have the first example of a disease thought to be bladder neck obstruction, but proving later to be nothing of the sort. But there are other serious cases which I would have originally labelled bladder neck obstruction yet which do not show fibro-elastosis and many other milder disorders in which the material for proving or disproving the case does not exist at present.

One source of confusion is the difficulty of judging what is good evidence of obstruction in the bladder. Trabeculation usually indicates detrusor hypertrophy and therefore an increased resistance to the outflow of the urine, but any child with severe frequency, even if it is of the enuretic type, may exhibit mild trabeculation and I cannot agree that all these have bladder neck obstruction for so many get well on a training regime. Residual urine is a traditional measure of the severity of the obstruction and when considerable in volume, as in the case of fibro-elastosis, provides indisputable evidence. But in infants whose micturition seldom occurs to order, and who may very well stop before the bladder is empty if their attention is distracted, residual urine cannot be measured with accuracy. Moreover, we find that in certain conditions the bladder empties itself completely but some of the urine is expelled into diverticula or into dilated ureters, whence it returns as soon as the detrusor relaxes; catheterization in such cases after micturition will withdraw a considerable volume of urine, but it will be a false rather than a true residual and does not necessarily indicate an obstruction to urine outflow. The case of the vesical diverticulum is of some importance and here again the diagnosis of bladder neck obstruction has sometimes been made in error. It is true that diverticula are usually a complication of some type of obstruction but in a few children the bladder appears to be otherwise normal and all the symptoms are relieved by excision of the diverticulum. The presence of the diverticulum, however, leads to a very considerable interference with the mechanism of bladder emptying and therefore to detrusor hypertrophy. The internal sphincter then thickens along with this hypertrophy and appears to reinforce the diagnosis of bladder neck obstruction. In two cases of vesical diverticula without other evidence of obstruction, biopsy of the anterior urethral wall has shown no fibro-elastosis, supporting the clinical impression that occasionally the primary disorder is a weakened area in the bladder muscle: this allows the herniation of mucosa which constitutes the diverticulum and all other changes are secondary. In one case I have observed this weakness before there was any permanent herniation; the mucosa was pushed out only during bladder contractions.

The same type of interference with bladder function occurs when there is free reflux into a dilated ureter. Occasionally one ureter is affected, often one of a pair of double ureters. A boy was sent up as a case of chronic retention of urine, the bladder being palpably distended after micturition. Cystograms, however, showed reflux into an enormous ureter and nephro-ureterectomy alone corrected his bladder disorder.

Often, however, the reflux is bilateral and occurs in the mega-ureter-megacystis syndrome. This term is one which I use to describe a comparatively common disorder of childhood, characterized by chronic bilateral hydro-ureter, a large capacity bladder, with free vesico-ureteric reflux and widely dilated ureteric orifices. Most of the children present with persistent pyuria but a few are first suspected of the obstruction because the bladder is palpably distended or there may be a transient acute retention of urine. The syndrome was at one time held to be due to a diminution in the number of ganglion cells in the bladder wall and therefore analogous to Hirschsprung's disease, but Dr. Leibowitz (1957) has made accurate counts in two of my post-mortem cases and found a normal ganglion cell population. At present we have not been able to put forward a satisfactory explanation of the pathology of this condition but it does seem that there is a disorder both of the bladder and of the ureters. Despite the large capacity bladder which can be demonstrated on cystometrograms, or more simply by watching the child pass a very large quantity of urine at one sitting, the bladder contraction does appear to obliterate the lumen. A large volume is, however, driven upwards into the ureters and by the time the child is examined this will have returned to the bladder, producing a palpable distension. It is therefore not surprising that many of these cases have been labelled bladder neck obstruction; they have

an apparently large residual urine, dilated ureters and even, in very severe cases, slight trabeculation, yet no obstruction can be found in the urethra. In two cases in which I have taken a biopsy of the anterior urethral wall there has been no sign of fibro-elastosis, but there are many other points of distinction from the typical fibro-elastosis cases. The mega-ureter-megacystis syndrome occurs at least as often in girls as in boys, the bladder capacity is large, reflux occurs early and into ureters which despite their size retain a surprising motility when observed on the cine film or on endoscopy. Most important of all from the clinical point of view is the distinction of false from true residual by double micturition. In the case of diverticulum without obstruction or of the megacystis syndrome, the second micturition, performed five or ten minutes after the first, will produce a considerable volume of urine and a third attempt may still produce something. By contrast, when there is a true residuum due to obstruction to the outflow, double micturition will not be possible. This simple test should be tried whenever a child is found with a palpable residual urine and although not infallible its results will usually set the investigations off along the right lines.

I have therefore described three diseases, urethral fibro-elastosis, primary vesical diverticulum and mega-ureter-megacystis which might all be taken for bladder neck obstruction. What then is there left? As far as my own practice is concerned the remainder are all rather unsatisfactory cases: there have been several enuretic girls, some with pyuria, with a residual urine which was curiously variable, and a normal upper urinary tract. In some a considerable improvement was obtained by an endoscopic resection of the bladder neck which did not seem to have removed enough to be of value. One or two resistant enuretics had evidence of bladder neck hypertrophy but no other abnormality—they improved without resection.

The neurogenic bladders due to spinal cord and cauda equina lesions I exclude from the category altogether: although in many there is a large residual urine and bladder neck hypertrophy, the disorder is one which affects the whole of bladder function, and is not a localized obstruction.

Several children had obstinate constipation as well as a residual urine, yet seemed to achieve normal bladder function when the rectum was kept constantly empty for some weeks.

REFERENCES

BODIAN, M. (1957) *Brit. J. Urol.*, **29**, 393.
KJELLBERG, C. S. R., ERICSSON, N. O., and RUDHE, U. G. (1957) The Lower Urinary Tract in Childhood. Chicago.
LEIBOWITZ, S. (1957) Personal communication.
MILLER, A. (1956) *Proc. R. Soc. Med.*, **49**, 895.

## *Bacillus fœcalis alcaligenes* Septicæmia in the Newborn

By S. A. DOXIADIS, M.D.,

with the co-operation of M. PAVLATOU, M.D., and O. CHRYSSOSTOMIDOU, M.D.

*From the University and State Alexandra Maternity Hospital (Director: Professor N. Louros), Athens, Greece*

ABOUT three years ago I saw in my unit, which is the neonatal and premature baby unit of a large teaching Maternity Hospital in Athens, a baby with an unusual redness on his face. The red area was very slightly raised and it was well delineated from the surrounding skin. It covered about half of the face and extended to the neck. The skin was bright red and it had a shiny appearance. The whole picture very much resembled an erysipelas and this was my first diagnosis. Penicillin was immediately given, but the redness spread and the baby died. Since, however, the baby also had hypoxia, death was attributed to that condition. In the following months we saw babies with similar red areas, looking like erysipelas and in all of them—although all did not die—penicillin did not make any difference. I was naturally surprised by this complete failure of penicillin to influence the course of a condition due to the hæmolytic streptococcus and with my assistants, who by that time were thoroughly familiar with this syndrome, began looking for other causes. There was no doubt in my mind that this was an infective process and we therefore started doing blood cultures on all the babies. The results were surprising because in nearly all the blood culture revealed the presence of a Gram-negative bacterium which on further study was identified as *Bacillus fœcalis alcaligenes*.

Only isolated cases of bacteriæmia due to this germ have been reported and in all the literature available to me I have been unable to find any series of cases or any description of this peculiar clinical manifestation. In the last three years we have been able to study 25 infants suffering from a bacteriæmic illness due to *B. fæc. alcaligenes* and showing the typical red area on their skin.

Table I gives the material on which the present study is based.

TABLE I.—MATERIAL

| | |
|---|---|
| Infants with positive culture for *B. fæc. alcaligenes* and erysipelatoid red areas | 28 |
| Infants with positive culture for *B. fæc. alcaligenes* and no red areas.. .. | 4 |
| Infants with red areas and blood cultures positive for other organisms .. | 4 |
| Infants with red areas and no blood culture .. .. .. .. .. | 16 |

There were 16 infants with typical skin manifestations but in whom blood culture was not done either because they were seen before we began taking blood from all suspect babies or because they died before blood was taken or finally because we failed to obtain any blood for technical reasons. Of the remainder, 28 had the typical red areas and positive blood cultures for *B. fæc. alcaligenes* while 4 had the bacteriæmia but not the skin manifestation. Finally there were another 4 infants with erysipelas-like areas on their skin clinically indistinguishable from those of the others but in whom the blood culture showed the presence of other organisms. In 2 the organism was *Pseudomonas aeruginosa*, in one *Bacterium coli* and in the fourth *Proteus*.

The observations which follow are based on the two groups with proved bacteriæmia due to *B. fæc. alcaligenes*, and mainly on the group of 28 infants who also showed the typical red patches.

TABLE II.—SEX, BIRTH WEIGHT AND MODE OF DELIVERY

Boys .. .. 22 Girls .. .. 10

| | | | | | |
|---|---|---|---|---|---|
| *Weight:* | Under 1,500 grams .. | 4 | *Delivery:* | Normal .. .. .. | 19 |
| | 1,501–2,000 grams .. .. | 2 | | Breech .. .. .. | 5 |
| | 2,001–2,500 grams .. .. | 9 | | Forceps .. .. .. | 6 |
| | Over 2,501 grams .. .. | 17 | | Cæsarean .. .. .. | 2 |

Table II shows the sex, birth weight and mode of delivery. In considering the weight groups it is not surprising that about half are prematures since their susceptibility to infection is well known, but that such a bacteriæmia also affected 17 full-term infants is surprising.

Now in trying to describe the clinical entity which is due to an infection of the blood stream by this bacillus, it is essential to eliminate all other possible causes of illness. For this reason I chose 13 babies who on clinical grounds may be considered "pure" cases, as distinguished from the remaining 15 in whom a preceding or associated illness obscured the picture of the septicæmia. In the first group the condition of the baby at birth was good or became good after a transient and mild difficulty while in the second group the condition after birth was not good because of either anoxia or birth injury or both. In these babies the signs of the septicæmia were added to those of the anoxia or the cerebral damage and it was not possible to say when the infection began (Table III).

TABLE III.—CONDITION AT BIRTH AND NUMBER OF DEATHS

| | | | |
|---|---|---|---|
| Good .. .. | 13−3=10 | Died .. .. | 4 |
| Not good .. | 15 | Died .. .. | 9 |
| Anoxia, birth trauma | | | |

The clinical course and the results of the autopsy compelled me to take away from the first group three babies. 2 showed at autopsy small intracranial hæmorrhages not detected or suspected during life and in one the autopsy revealed a severe congenital malformation of the heart. There were left therefore 10 babies in whom, as far as we could tell, there was no other illness except the septicæmia due to *B. fæc. alcaligenes*. One of those babies was just under 3 lb. (1,300 grams), 7 were 4½–5½ lb. (2,050–2,500 grams) and 2 were above 5½ lb. The clinical picture of the *B. fæc. alcaligenes* septicæmia in these "pure" cases was in no way different from any other septicæmic illness of the neonatal period with one exception, that of the red patches on the skin. This sign appeared between the third and seventh days of life.

It was the first and only sign of the illness in two babies. Both were immediately treated with chloramphenicol and they survived. In the other 8 babies general symptoms and signs either preceded the appearance of the skin manifestations by twenty-four hours or appeared on the same day. These general signs were those of any infection, i.e. listlessness and difficulty in feeding in all, cyanotic attacks in 3, periods of apnœa in 2 and convulsions in 1. The temperature was significantly raised in only 3 babies. The white blood count, when taken, showed a normal total count but with a definite preponderance of the myeloid series. In only one baby we found a total count of 44,000 per c.mm. The baby died later in another hospital, autopsy was not done and I do not know if there was any other reason for such a high white blood count.

It is of great interest that diarrhœa was present in only 2 of all the 32 babies with a positive blood culture.

The peculiar red areas appearing in the skin are bright red and well delineated, the skin is sometimes very slightly raised, only occasionally indurated. The area of the skin initially affected may be anywhere (Table IV), but in most cases the region favoured was the face and the neck. The shape often changed from day to day, sometimes even from hour to hour. Usually there was an extension of the red area for a day or two and then it began to fade. In other cases new red patches appeared in other remote areas of the body. The fading was not always, however, a good prognostic sign, because it was also seen in babies whose condition deteriorated and who died. In three cases a section of the affected skin was taken a few hours after death and examined histologically. There were no detectable changes. This negative finding together with the quick changes in shape and localization suggest that this is a vasomotor phenomenon and not a real inflammation as in erysipelas.



FIG. 1.

TABLE IV.—INITIAL LOCALIZATION OF RED AREAS

| | |
|---|---|
| Face .. .. .. | 6 |
| Neck .. .. .. | 8 |
| Groins .. .. .. | 2 |
| Buttocks .. .. | 3 |
| Umbilicus .. .. | 4 |
| Lower abdomen .. | 1 |
| Abdomen and thigh .. | 1 |
| Face and chest .. | 1 |
| Ankles .. .. .. | 1 |
| Neck and thigh .. | 1 |

I have been able to photograph only one of these last cases. This is a 3 lb. baby (Fig. 1), who was well till the third day of life when the first redness appeared on the face. The following day the redness had spread to the abdomen and the thighs. The blood culture for *B. fæc. alcaligenes* was positive. The baby died on the sixth day.

All strains of *B. fæc. alcaligenes* cultured from the blood were tested for their sensitivity to antibiotics. They were resistant to all. One only showed a slight sensitivity to chloramphenicol and Albamycin and very slight to Aureomycin. In spite of these results antibiotics were given to all the babies. Some of them, especially those seen at the beginning, received penicillin and streptomycin, others antibiotics of the tetracycline group, but all except 5 at some stage received chloramphenicol because the clinical impression had been gained that it was the antibiotic most likely to help. However, there were so many other factors affecting the outcome that I am not certain that the chloramphenicol was really superior. Nevertheless, when reviewing these cases the initial impression that chloramphenicol is the drug of choice was reinforced.

Of the 32 babies with a positive blood culture 19 died. Death occurred between twelve hours and eleven days from the appearance of the red patches. An autopsy was performed on 8 babies. In 2 there was severe malformation of the heart, in one hyaline membrane disease and in 2 cerebral hæmorrhage. The findings which could be attributed to the septicæmia were purulent pericarditis in 2 and meningitis in 1—with growth of the *B. fæc. alcaligenes* from the pus or the cerebrospinal fluid. One other baby developed meningitis five days after the first redness of the skin, but it survived and was left with hydrocephalus. There was also pneumonia in 3 of the babies and suprarenal hæmorrhage in 1 but I cannot say that they were due to the septicæmia.

Trying to find what may affect the progress one is impressed by only one factor, an obvious one: the presence of any associated illness such as birth injury or anoxia. Thus, as already shown, 4 of the 10 uncomplicated, so to speak "pure" cases died, while of the remaining 22, 15 died.

I have tried to describe an ætiological entity—septicæmia of the newborn due to *B. fæc. alcaligenes*, of which I had the chance to study a large number of cases. I have also suggested that the septicæmic illness has—in addition to the symptoms and signs of a general infection

—a peculiar clinical manifestation, the red patches of the skin, and that these occur in such a high proportion of cases (28 of 32) as to make the diagnosis very likely on clinical grounds alone. That this sign is not absolutely specific and pathognomonic is shown by the fact that at the same time we saw four babies with septicæmia due to other organisms, who clinically resembled the group of the *B. fæc. alcaligenes* septicæmia. It may be that we are dealing with a non-specific vasomotor reaction which is due almost always to one specific cause. One is reminded of the erythema nodosum that some years ago used to be, in about 80% of the cases in children, a manifestation of primary tuberculous infection. This is, however, a matter of surmise.

Another question arising from this study is the high incidence of this septicæmia. Why is it that in our Maternity Hospital with over 6,000 births per year we have seen so many cases while in the literature one finds reports of one or two cases—mostly in adults? There have so far been recorded only 5 cases of a generalized infection possibly due to this organism in newborn infants and in all there has been meningitis. Could it be that this septicæmia is commoner than we thought as we are not yet doing frequent blood cultures in the neonatal period; or that when a Gram-negative organism is found we tend to consider it as a contaminant? On the other hand it is unlikely that this striking skin manifestation could have been missed. There is no mention of anything similar in the literature available to me. Perhaps in the pre-penicillin days it might have been considered as true erysipelas.

I was very interested to see the description of a condition called red-leg occurring in frogs (Miles, 1950), which can be caused by many other organisms and the *B. fæc. alcaligenes*. The clinical description of red-leg, however, does not give the impression of a vasomotor phenomenon but of an acute inflammation.

I have to add that in my material, although I had cases occurring in the same room in babies lying close by, I have not been convinced that there was a transmission. But then why should an organism of very mild virulence invade the blood stream of a normal, even small, neonate? That Hirst's (1917) theory, according to which diarrhœa makes the invasion from the bowel easy, does not apply here is obvious from the fact that in only 2 of the 32 babies was diarrhœa present. On the other hand none of these babies was fully breastfed.

REFERENCES

HIRST, L. F. (1917) *J.R. Army med. Cps*, **29**, 476.
MILES, E. M. (1950) *J. gen. Microbiol.*, **4**, 434.

## Cutaneous Gangrene

By K. W. LOVEL, M.R.C.P.
*Oxford*

THIS subject was chosen because it is a meeting point of pædiatrics with surgery, dermatology and angiology, and because in recent years a number of new types of gangrene have been observed.

Because of its striking appearance, gangrene has attracted attention from the earliest times, but the first complete treatise on the subject was written by Fabricius Hildanus in 1593. This author described gangrene of the newborn due to pressure during delivery, and regarded cancrum oris as a complication of infantile scurvy. He considered gangrene to be a form of *inflammation* which could proceed to mortification, i.e. what would to-day be called "threatened gangrene". Nowadays, gangrene implies tissue death combined with putrefaction, usually due to saprophytes, and the colours and odours of gangrene are the result of decomposition of blood and other tissues by these organisms. They do not tend to invade adjacent healthy tissue, but occasionally gangrene is caused by pathogens and is then liable to spread rapidly. Besides the well-known gas-forming organisms, the combination of streptococci with staphylococci seems particularly virulent, giving what Meleney (1931) has called "bacterial synergistic gangrene", and some of the outbreaks of "hospital gangrene" reported in the last century may have been due to this cause. It follows that gangrene is most likely to occur in tissues to which organisms normally have access: the skin, mucous membranes, lungs and intestines. This paper, however, is only concerned with the more superficial forms of gangrene.

### CLASSIFICATION

Slides were then shown to illustrate types of gangrene due to infection, trauma (Fig. 1) renal disease, intra-arterial injections, intravenous infusion (Fig. 2), polyarteritis nodosa, arterial thrombosis and embolism, hæmorrhage (Fig. 3), arteriovenous aneurysm, "pink disease" and Raynaud's disease. On the basis of these and other published cases, the following classification of gangrene was proposed (Table I).



FIG. 1.—Gangrene of the tip of the nose due to repeated scratching, in a mentally defective child.



FIG. 2.—Gangrene following an intravenous infusion containing l-noradrenaline (Levophed).



FIG. 3.—Gangrene of four toes due to meningococcal septicæmia with purpura.

TABLE I.

| Pathology | Clinical types | Reference |
|---|---|---|
| Tissue destruction .. | Cancrum oris and other local infections. Gangrene due to injuries, cold, thermal, chemical and electrical burns, snake and scorpion bites, subcutaneous injections | Luder (1955)<br>M.R.C. (1944)<br>Lucan (65)<br>Ansari (1948)<br>Coles and Douglass (1955) |
| Circulatory stasis .. | Terminal | Lowe (1954) |
| Circulatory diversion .. | Arteriovenous aneurysm | Allen *et al.* (1955) |
| Arterial inflammation .. | Generalized infections<br>Polyarteritis nodosa<br>Disseminated lupus<br>Henoch-Schönlein syndrome<br>Acute nephritis<br>Thrombo-angiitis obliterans | Martin and Shore (1928)<br>Neale (1949)<br>Keat and Shore (1958)<br>Taylor and Jacoby (1949)<br><br>Wigglesworth (1953) |
| Arterial spasm .. .. | Ergot poisoning<br>Raynaud's disease<br><br>Pink disease<br>Noradrenaline infusions | Barger (1931)<br>Raynaud (1862)<br>Lewis and Pickering (1934)<br>Debré and Lelong (1952)<br>Humphreys *et al.* (1955) |
| Arterial degeneration .. | Diabetic<br>Arteriosclerotic | Lawrence and McCance (1931) |

| Pathology | Clinical types | Reference |
|---|---|---|
| Arterial compression .. | Over-use of tourniquets and splints: coagulation treatment of encircling burns | Martin *et al.* (1956)<br>McIndoe and Watson-Jones (1944) |
| Arterial thrombosis and embolism .. .. | Intra-arterial injections<br>Cyanotic congenital heart disease | Cohen (1948)<br>Schlesinger and MacCarthy (1953) |
| Extensive venous thrombosis | Phlegmasia cærulea cruris | Haimovici (1950) |
| Subcutaneous hæmorrhage | Purpura | Sheldon (1947)<br>Dunn (1951) |

## Prevention and Treatment

Many of the cases have occurred in children who have been malnourished, neglected or dehydrated, and the best prophylaxis of gangrene lies in the prevention of these conditions. Arterial injections should be avoided as far as possible, and limbs into which intravenous infusions are being given should be inspected at frequent intervals. The necessity for immobilizing the limb may be reduced by using plastic tubing rather than a cannula, or the infusion may be given by a fine needle into a scalp or other vein.

Acute bacterial infections should be treated by appropriate drugs, including steroids, and varicella and vaccinia gangrenosa by gamma-globulin. Threatened gangrene should be treated by elevation of the affected limb (but cooling may still further impair the circulation by encouraging venous stasis and thrombosis), and where thrombosis is suspected, anticoagulant therapy is indicated. To improve the collateral circulation heat should be supplied to the rest of the body, and vasodilator drugs such as aspirin, alcohol, papaverine and tolazoline (Priscol) should be used, but it must not be forgotten that sleep is the best natural vasodilator, and it may be necessary to give analgesics and sedatives to ensure this.

For established gangrene, amputation is seldom necessary and never urgent in the absence of spreading sepsis (Greene, 1941). If, however, gangrene appears to be spreading, or if there is constitutional disturbance, antibiotic treatment and early excision of the affected area may save life and limb.

The author expressed his thanks to Dr. Victoria Smallpeice, Dr. Hugh Ellis, and Dr. Wilfrid Sheldon for permission to quote details of their cases, and to Mr. E. L. Tugwell and Mr. Derek Martin for some of the photographs.

## References

Allen, E. V., Barker, N. W., and Hines, E. A. (1955) Peripheral Vascular Diseases. 2nd ed. Philadelphia and London; p. 419.
Ansari, M. Y. (1948) *Brit. med. J.*, ii, 388.
Barger, G. (1931) Ergot and Ergotism. London and Edinburgh; p. 59.
Cohen, S. M. (1948) *Lancet*, ii, 361 and 409.
Coles, R. B., and Douglass, W. M. M. (1955) *Brit. med. J.*, ii, 660.
Debré, R., and Lelong, M. (1952) Pédiatrie. Paris; p. 1913.
Dunn, H. G. (1951) *Arch. Dis. Childh.*, **26**, 184.
Fabricius Hildanus (1600) De Gangraena et Sphacelo. Cologne; III, 4 and 6.
Greene, R. (1941) *Lancet*, ii, 689.
Haimovici, H. (1950) *Circulation*, **1**, 225.
Humphreys, J., Johnston, J. H., and Richardson, J. C. (1955) *Brit. med. J.*, ii, 1250.
Keat, E. C. B., and Shore, J. H. (1958) *Brit. med. J.*, i, 25.
Lawrence, R. D., and McCance, R. A. (1931) *Arch. Dis. Childh.*, **6**, 343.
Lewis, T., and Pickering, G. W. (1934) *Clin. Sci.*, **1**, 327.
Lowe, K. G. (1954) *Lancet*, ii, 780.
Lucan (65), Pharsalia. Tr. Graves, R. London (1956); IX, 767.
Luder, J. (1955) *Gt. Ormond St. J.*, No. 9, 22.
McIndoe, A., and Watson-Jones, R. (1944) *Lancet*, i, 738.
Martin, P., Lynn, R. B., Dible, J. H., and Aird, I. (1956) Peripheral Vascular Diseases. Edinburgh and London; p. 547.
Martin, W., and Shore, B. R. (1928) *Ann. Surg.*, **88**, 725.
*M.R.C. (War) Memor.* (1944) No. 13. Arterial injuries.
Meleney, F. L. (1931) *Ann. Surg.*, **94**, 961.
Neale, A. V. (1949) *Arch. Dis. Childh.*, **24**, 224.
Raynaud, A. G. M. (1862) De l'Asphyxie Locale, et de la Gangrène Symétrique des Extrémités. Paris.
Schlesinger, B., and MacCarthy, D. (1953) In: Garrod, Batten and Thursfield's Diseases of Children. 5th ed. London; p. 1003.
Sheldon, J. H. (1947) *Arch. Dis. Childh.*, **22**, 7.
Taylor, A. W., and Jacoby, N. M. (1949) *Lancet*, ii, 792.
Wigglesworth, R. (1953) *Proc. R. Soc. Med.*, **46**, 275.

# Section of Urology

President—LESLIE N. PYRAH, M.Sc., Ch.M., F.R.C.S.

[*April* 25, 1958]

MEETING AT THE GENERAL INFIRMARY, LEEDS

## The Causes of Death in 14 Cases of Acute Renal Failure [*Summary*]

By C. K. ANDERSON, M.B.

*Leeds*

THE clinical course of 14 patients who died with acute renal failure after treatment by hæmodialysis on the Kolff-Brigham artificial kidney were described.

The precipitating factor in the 14 cases was as follows: Surgical procedures 9 cases, hepato-renal syndrome 3 cases, aortogram 1 case, road accident 1 case. The renal lesion most commonly encountered was of extreme severity with necrosis of proximal and distal convoluted tubules and thrombi in the glomerular tufts.

In 6 instances the renal lesion was of severe type with 2 patients showing signs of healing and clinical recovery. In a further 3 cases the lesions were less severe in type and of more patchy distribution.

One patient had suppurative pyelonephritis and another multiple pyæmic abscesses in the kidneys.

One patient had moderate nephrosclerosis as a result of active hyperparathyroidism due to a parathyroid adenoma.

In 2 patients the kidneys were histologically normal.

The most common complication in these patients was sepsis, which was the principal cause of death in 7 patients and a contributory factor in 2 others, one of whom died as a result of a perforation of a duodenal ulcer and the other from hæmorrhage from an acute gastric erosion.

In the remaining 5 patients death was attributed to the metabolic disturbance produced by the renal failure.

It was concluded that owing to the protean nature of the renal lesions encountered, the term acute renal failure is to be preferred to that of tubular necrosis. In the uræmic patient all complications are of serious import, but sepsis is peculiarly liable to prove fatal.

## The Genesis of Tumours of the Bladder and Other Tissues with Special Reference to the Industrial Amines

By G. M. BONSER, M.D., F.R.C.P., M.R.C.S., D. B. CLAYSON, B.A., Ph.D., J. W. JULL, B.Sc., Ph.D., and L. N. PYRAH, M.Sc., Ch.M., F.R.C.S.

*Department of Experimental Pathology and Cancer Research and Department of Urology, University of Leeds*

THE German urologist Rehn in 1895 observed that a number of cases of carcinoma of the bladder presenting themselves at his clinic came from one chemical factory. This has been followed by reports from every country with an established chemical industry that workmen engaged in making certain chemical intermediates are more liable to bladder cancer than the rest of the population. The many hundreds of chemicals handled by the industry, the long latent period of the tumours and the lack until quite recently of any means of reproducing the disease in experimental animals were among the factors which made it extremely difficult to be certain which substances were responsible for the human disease. Case and his colleagues (Case *et al.*, 1954; Case and Pearson, 1954) as a result of a field survey sponsored by the Association of British Chemical Manufacturers were able to show that although aniline was innocuous in this respect, the manufacture of 1- and 2-naphthylamine, benzidine, auramine and magenta was hazardous. A more recent report from America (Melick *et al.*, 1956) has shown that 4-aminodiphenyl (xenylamine) is also extremely dangerous. Fortunately this compound has not been made or used on a large scale in this country.

The existence of this human hazard poses three questions to the experimentalist: How and why do the bladder tumours arise? What other chemicals are likely to be hazardous if brought into large scale production? What bearing, if any, have the findings on the industrial hazard on the spontaneous human disease? It is the purpose of this paper to give some account of the attempts which have been made in Leeds and elsewhere to answer these questions.

The first problem was to attempt to reproduce the human disease in the experimental animal. After many years of arduous and fruitless work in many parts of the world, Hueper and Wolfe (1937) demonstrated that 2-naphthylamine, when given to the dog in relatively high doses for from two to five years, induced tumours of the bladder which resembled the human disease in all respects. Hueper used the commercial chemical. Bonser has since twice repeated the experiment using firstly a partially purified sample of 2-naphthylamine (Bonser, 1943) and latterly a sample purified at the Royal Cancer Hospital by one of the most rigorous means available (Bonser, Clayson, Jull and Pyrah, 1956). This successful repetition of Hueper's work suggests that 2-naphthylamine and not some impurity in it is responsible for the bladder tumours.

Attempts to reproduce the industrial disease in other experimental animals with 2-naphthylamine have been less successful (Table I). In all cases the maximum tolerated dose

TABLE I.—INDUCTION OF TUMOURS WITH ORALLY ADMINISTERED 2-NAPHTHYLAMINE

| Species | Bladder tumours | Liver tumours |
|---|---|---|
| Dog | E.P.C. | — |
| Mouse (CBA) | — | C. |
| Rat | P. | — |
| Rabbit | E. | — |
| Cat | — | — |

E=early changes; P=papillomas; C=carcinomas.

of the chemical was fed for as great a portion of the life-span of the animal as possible. In the mouse a 40% yield of hepatomas but no bladder cancers were obtained, in the rat and rabbit (Bonser *et al.*, 1952) only benign changes were observed in the bladder, whereas the cat, which will only tolerate small doses of the chemical, was completely negative (Bonser, unpublished observation). These experiments illustrate the marked species variation in response to a chemical.

Another amine, whose dangerous nature was discovered before it came into use as an insecticide—2-acetylaminofluorene—illustrates the very important fact that these amines are not limited in their action to the bladder only. This compound (Table II) induces tumours at

TABLE II.—SITE OF ELECTION OF TUMOURS INDUCED BY 2-AMINOFLUORENE AND 2-ACETYLAMINOFLUORENE

| | Site of tumours | | | | | | |
|---|---|---|---|---|---|---|---|
| Species | Bladder | Liver | Intestine | Kidney | Breast | Local | Others |
| Dog .. | + | + | — | — | — | — | — |
| Cat .. | — | + | — | + | — | — | + |
| Rat .. | + | + | + | + | + | + | + |
| Mouse .. | + | + | — | + | + | — | + |
| Rabbit .. | + | — | — | — | — | — | + |
| Fowl .. | — | — | — | + | — | — | — |

many sites in the experimental animal and should lead us to the conclusion that amine-induced tumours in man are to be expected in sites other than the bladder. These two examples of the induction of tumours by aromatic amines could be multiplied many times as a result of the past twenty years' work in many parts of the world.

The biological results must serve as the basis for the biochemical investigation of the problem. At the start of our chemical studies in Leeds it was decided that it was most rational to assume that the effective carcinogen in the induction of bladder tumours by 2-naphthylamine was more likely to be urine-borne than blood-borne. It was also considered likely that a metabolite, rather than the amine itself, induced the tumours. The urogenous nature of 2-naphthylamine tumours in the dog has since been demonstrated by McDonald and Lund (1954) who prepared bladder pouches in dogs and fed the chemical. All the tumours observed were located in the bladder unless the pouches were defective and urine leaked in.

In 1948 we knew from the work of Wiley (1938) that in the dog 2-naphthylamine gave 2-amino-1-naphthyl hydrogen sulphate, whereas Dobriner *et al.* (1941) had shown that in the rat, rabbit and monkey 2-acetamido-6-naphthol was a metabolite. Two courses were open,

either the metabolism of 2-naphthylamine could be investigated intensively in one species or one aspect of its metabolism could be chosen for a wider survey. The latter course was adopted.

A method was devised for the estimation of 2-amino-1-naphthol and its conjugates in urine and was applied to as many species as possible. In the dog some 30–70% of a dose of 2-naphthylamine was excreted in the urine as conjugates of 2-amino-1-naphthol. All the other species (Fig. 1) excreted less of the dose in this form. On the basis of the biological

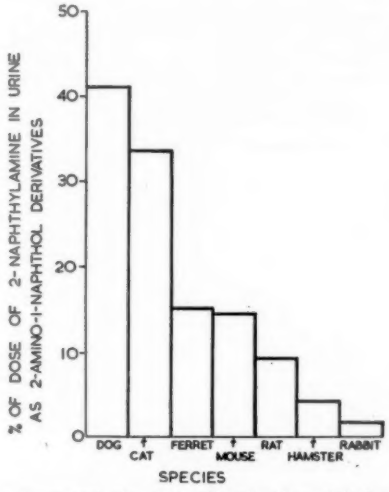



FIG. 1.—Variation in output of urinary 2-amino-1-naphthol conjugates when 2-naphthylamine is administered to various species of experimental animals.

results then available there appeared to be a parallel between the amount of the dose excreted in the form of 2-amino-1-naphthol and its conjugates and the biological potency of 2-naphthylamine in the dog, mouse, rat and rabbit (Bonser *et al.*, 1951). It was concluded that 2-amino-1-naphthol and its conjugates might be of great importance in the induction of tumours by 2-naphthylamine. This idea was strengthened when it was discovered that in the dog the plasma level of 2-amino-1-naphthol and its conjugates was at the level of detection and that these substances had a urine plasma ratio of about 200 to 1. This we felt was a possible reason why the tumours with 2-naphthylamine were not widespread but were concentrated in the urinary tract where the suspected carcinogen was at its highest level.

The conventional methods of testing chemicals for carcinogenic activity gave only negative or equivocal results with water soluble labile compounds of the nature of 2-amino-1-naphthol. Jull (1951) suggested and developed the method of bladder implantation. The chemical was intimately mixed with an inert vehicle and the mixture made into pellets of weight about 15–25 mg. by melting or compression. A pellet was then implanted surgically into the lumen of the bladder of each mouse. After forty weeks the animals were killed, the bladders distended with fixative and examined both macroscopically and microscopically for tumours. Under these conditions some compounds gave a good incidence of tumours; others, and the vehicle alone, gave much lower yields of tumours. The results obtained with 2-naphthylamine and its derivatives are shown in Table III (Bonser, Bradshaw, Clayson and Jull, 1956).

TABLE III.—THE RESULTS OF THE BLADDER IMPLANTATION OF 2-NAPHTHYLAMINE AND ITS DERIVATIVES

| Compound | Number of survivors | Number with carcinomas | P. |
|---|---|---|---|
| Vehicle alone .. .. .. .. | 56 | 2 | — |
| 2-Naphthylamine .. .. .. .. | 89 | 8 | 0·18 |
| 2-Amino-1-naphthol hydrochloride .. | 118 | 20 | 0·009 |
| 2-Amino-1-naphthyl hydrogen sulphate .. | 38 | 2 | 0·53 |

Whereas the vehicle alone gave a very low yield of tumours, and the simple amine a slightly higher yield, 2-amino-1-naphthol in the form of its hydrochloride gave a significantly higher

yield. It is interesting to notice that the sulphuric acid derivative which gave a low yield of tumours when implanted in paraffin wax appears to be slightly active in another vehicle—cholesterol.

All this evidence suggests that 2-amino-1-naphthol is a carcinogenic metabolite of 2-naphthylamine. If this is true, it follows that similar carcinogenic metabolites of other carcinogenic amines ought to exist. The typical carcinogenic aromatic amines (Fig. 2) have

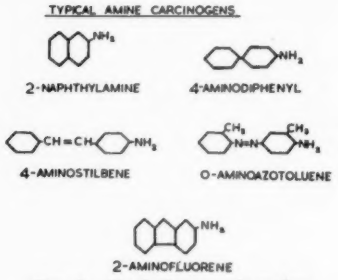



FIG. 2.—Typical aromatic amine carcinogens.

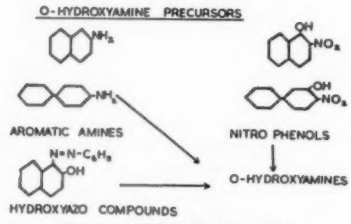



FIG. 3.—*Ortho*-hydroxyamine precursors.

one structural feature in common, the position *para* to the amino-group is blocked by a large substituent. As amines are hydroxylated in the *ortho* and *para* positions during the course of their metabolism in the animal body, it seems likely that if the *para* position is blocked the *ortho* position is more likely to be hydroxylated. Clayson (1953) suggested that certain *ortho*-hydroxyamines, i.e. chemicals like 2-amino-1-naphthol, would prove to be carcinogenic and that the carcinogenic aromatic amines would be more readily converted to *ortho*-hydroxyamines than those which were not carcinogenic.

Use of the bladder implantation technique has so far tended to confirm the first prediction that *ortho*-hydroxyamines are carcinogenic. Only one further example will be quoted. 4-Aminodiphenyl and its derivatives (Table IV) (Bonser, Bradshaw, Clayson and Jull, 1956)

TABLE IV.—THE RESULTS OF THE BLADDER IMPLANTATION OF 4-AMINODIPHENYL AND ITS DERIVATIVES

| Compound | Number of survivors | Number with carcinomas | P. |
|---|---|---|---|
| Vehicle alone .. .. .. .. .. | 56 | 2 | — |
| 4-Aminodiphenyl .. .. .. .. | 35 | 3 | 0·29 |
| 3-Hydroxy-4-aminodiphenyl sulphate .. | 38 | 9 | 0·004 |
| 4-Amino-3-diphenylyl sodium sulphate .. | 21 | 1 | 0·62 |

behave similarly to the corresponding derivatives of 2-naphthylamine. The *ortho*-hydroxyamine is again the most potent bladder carcinogen on local application.

The next point it is necessary to demonstrate is that the *ortho*-hydroxyamines are actually present in the urine of animals which develop bladder cancer with the aromatic amines. In Leeds (unpublished observations) traces of free *ortho*-hydroxyamines have been shown to be present in twenty-four hour specimens of the urine of dogs dosed with 2-naphthylamine, 4-aminodiphenyl and benzidine although it has not been possible to demonstrate them in freshly voided urines. Dogs dosed with these amines develop bladder tumours readily in the former cases and with more difficulty in the case of benzidine. Weisburger *et al.* (1957) have shown that *ortho*-hydroxy derivatives of 2-acetylaminofluorene are present in the urine of rats but not of guinea-pigs treated with the chemical. Rats but not guinea-pigs are susceptible to the carcinogenic action of 2-acetylaminofluorene. Similarly, Daniel (1956) has shown that rabbits convert the orally ingested food dye oil orange E to 1-amino-2-naphthol. The results of an incomplete experiment suggest that this azo-compound may be a bladder carcinogen in the rabbit (Bonser, unpublished observation).

It appears from the evidence discussed above that aromatic amines are carcinogenic because they are converted into *ortho*-hydroxyamines which are liberated into the urine of susceptible species. The mechanism of the liberation of the free *ortho*-hydroxyamine from its conjugates in the urine is more complicated. Bonser *et al.* (1951) suggested that the aryl hydrogen sulphates were the precursors of the free *ortho*-hydroxyamines found in the urine, but Boyland *et al.* (1956) demonstrated that 2-amino-1-naphthyl hydrogen sulphate and several related sulphuric acid esters were not hydrolysed by mammalian sulphatases. They suggested that the glucuronides were the precursors of the free *ortho*-hydroxyamines found in the urine

and supported this by showing in one small group of mice that 2-amino-1-naphthyl glucuronide induced tumours on bladder implantation (Allen *et al.*, 1957).

This idea does help to clarify the position in a number of respects but still leaves several points to be settled. Although the cat excretes a considerable part of a dose of 2-naphthylamine as 2-amino-1-naphthol conjugates it has not proved possible to induce 2-naphthylamine tumours in this species. Recent evidence that the cat is deficient in the ability to form glucuronides would, in the light of Boyland's suggestion, explain this anomaly. On the other hand, Bradshaw (unpublished observation) has failed to detect any trace of a glucuronide in the urine of dogs dosed with 4-aminodiphenyl. The amine is one of the most potent bladder carcinogens in the dog and traces of 3-hydroxy-4-aminodiphenyl have been found in ether extracts of the urine. The position may be further clarified by the discovery of an alkaline labile phosphorus-containing derivative of 2-amino-1-naphthol in the urine of dogs dosed with 2-naphthylamine (Troll and Nelson, 1958). This new metabolite is readily split by phosphatase and is said to be present in considerable quantities. It will be interesting to see if similar metabolites can be shown to be present in urines of animals dosed with other bladder carcinogens.

The second question that was asked at the beginning of this paper was whether it was possible to predict what compounds were likely to be dangerous if handled indiscriminately. If, as the evidence appears to show, *ortho*-hydroxyamines are carcinogenic then any compound which might lead to an *ortho*-hydroxyamine in the body must be regarded with suspicion (Fig. 3). It is to be expected that the tumours will not always be in the bladder, as the site of election of the tumours will depend on the site at which the *ortho*-hydroxyamines reach their most effective concentration. Besides the aromatic amines, the *ortho*-nitro- and the *ortho*-nitrosophenols and the *ortho*-hydroxyazo-compounds may be reduced in the body to the potential carcinogens. The hydroxyazo-compounds are probably the most important as they are being used increasingly to colour food. There is a general impression that if these compounds are sufficiently water soluble they will be harmless. There does not seem to be any evidence in support of this; in fact, the little evidence available shows that at least one water-soluble compound—trypan blue—is a carcinogen. Although the position has been much improved in this country by recent legislation, there is still much left to be desired.

Boyland and his colleagues have made an attempt to apply the findings on the industrial disease to the problem of the spontaneous bladder tumours in man. Dunning *et al.* (1950) showed that rats fed a diet containing added tryptophan and 2-acetylaminofluorene developed a higher incidence of tumours of the bladder than did rats fed the chemical and a more normal level of tryptophan. Boyland *et al.* (1954) repeated this experiment and from a consideration of the metabolism of trytophan suggested that the increased incidence of bladder tumours in these experiments was due to the synergistic action of the *ortho*-hydroxyamines derived from the acetylaminofluorene and the tryptophan. Allen *et al.* (1957) then tested some of the metabolites of tryptophan by bladder implantation and found them to be carcinogenic. A major criticism of this work is that the numbers used are far too low for the confident acceptance of such an important result. The results for the *ortho*-hydroxyamines tested (Table V) are consistently higher than those for the metabolites which are not *ortho*-

TABLE V.—THE RESULTS OF THE BLADDER IMPLANTATION OF TRYPTOPHAN METABOLITES (Allen *et al.*, 1957)

| Compound | Number of survivors | Number with carcinomas |
|---|---|---|
| Vehicle alone .. .. .. .. .. | 24 | 1 |
| Kynurenic acid .. .. .. .. .. | 20 | 1 |
| 3-Hydroxykynurenine .. .. .. .. | 25 | 6 |
| 8-Methoxy-4-hydroxyquinoline-2-carboxylic acid | 19 | 3 |
| 3-Hydroxyanthranilic acid .. .. .. .. | 40 | 8 |
| 2-Amino-3-hydroxy-anthranilic acid .. .. | 17 | 4 |
| 5-Hydroxytryptamine creatinine sulphate .. | 14 | 0 |

hydroxyamines. If these results are confirmed on larger numbers, the proof that compounds arising in the course of normal metabolism can induce bladder cancer will mean a great step forward in our understanding of the spontaneous disease. If the plasma concentration of these *ortho*-hydroxyamine metabolites is significant it may be possible to comprehend the spontaneous genesis of other forms of cancer with more understanding than at present.

*Summary.*—The aromatic amines have been found to induce tumours of the bladder in men exposed to them in the course of their work. It is possible to reproduce the condition in experimental animals. The study of the fate of the amines in the animal body suggested that the derived *ortho*-hydroxyamines might be carcinogenic metabolites. This has been confirmed by the technique of bladder implantation and a working hypothesis evolved which

is not contra-indicated by the majority of the known facts. Using this working hypothesis it can be predicted that compounds which the body is able to convert to *ortho*-hydroxyamines may be carcinogenic and that these should not be allowed to come into contact with the human population. It is also apparent that, if *ortho*-hydroxyamines arise in the body as a result of normal or abnormal metabolism, some at least of the so-called spontaneous tumours in man may be explicable.

## REFERENCES


ALLEN, M. J., BOYLAND, E., DUKES, C. E., HORNING, E. S., and WATSON, J. G. (1957) *Brit. J. Cancer*, **11**, 212.

BONSER, G. M. (1943) *J. Path. Bact.*, **55**, 1.

——, BRADSHAW, L., CLAYSON, D. B., and JULL, J. W. (1956) *Brit. J. Cancer*, **10**, 539.

——, CLAYSON, D. B., and JULL, J. W. (1951) *Lancet*, ii, 286.

——, ——, ——, and PYRAH, L. N. (1952) *Brit. J. Cancer*, **6**, 412.

——, ——, ——, —— (1956) *Brit. J. Cancer*, **10**, 533.

BOYLAND, E., HARRIS, J., and HORNING, E. S. (1954) *Brit. J. Cancer*, **8**, 647.

——, MANSON, D., SIMS, P., and WILLIAMS, D. C. (1956) *Biochem. J.*, **62**, 68.

CASE, R. A. M., HOSKER, M. E., MCDONALD, D. B., and PEARSON, J. T. (1954) *Brit. J. industr. Med.*, **11**, 75.

——, and PEARSON, J. T. (1954) *Brit. J. industr. Med.*, **11**, 213.

CLAYSON, D. B. (1953) *Brit. J. Cancer*, **7**, 460.

DANIEL, J. W. (1956) *Biochem. J.*, **64**, 1P.

DOBRINER, K., HOFMANN, K., and RHOADS, C. P. (1941) *Science*, **93**, 600.

DUNNING, W. F., CURTIS, M. R., and MAUN, M. E. (1950) *Cancer Res.*, **10**, 454.

HUEPER, W. C., and WOLFE, H. D. (1937) *Amer. J. Path.*, **13**, 656.

JULL, J. W. (1951) *Brit. J. Cancer*, **5**, 328.

MCDONALD, D. F., and LUND, R. R. (1954) *J. Urol.*, **71**, 560.

MELICK, W. F., ESCUE, H. M., NARYKA, J. J., MEZERA, R. A., and WHEELER, A. P. (1956) *J. Urol.*, **74**, 760.

REHN, L. (1895) *Arch. klin. Chir.*, **50**, 588.

TROLL, W., and NELSON, N. (1958) *Fed. Proc.*, **17**, 324.

WEISBURGER, J. H., WEISBURGER, E. K., and MORRIS, H. P. (1957) *Science*, **125**, 503.

WILEY, F. H. (1938) *J. biol. Chem.*, **124**, 627.


# The Urinary Excretion of Oxalic Acid in Nephrolithiasis


By A. HODGKINSON, B.Sc., Ph.D., A.R.I.C.

*Medical Research Council Unit for Metabolic Disturbances in Surgery, The General Infirmary, Leeds*


Approximately two-thirds of renal stones which occur in this country contain calcium oxalate to greater or lesser extent. It is known that hypercalciuria plays an important part in the formation of many of these stones, but the possible role of hyperoxaluria has not been investigated to the same extent.

Most of the oxalic acid normally present in the urine appears to be derived from dietary oxalic acid. The proportion of ingested oxalic acid which is excreted in the urine depends in part on its availability; on whether, for example, it is present in the gut as the soluble sodium salt or the insoluble calcium salt. Excretion may be increased twofold if the intake of calcium is reduced from normal to low levels. A diet containing a preponderance of oxalate-containing vegetable foods and a deficiency of calcium-containing dairy foods favours a high urinary excretion of oxalic acid, and Grossmann (1938) considered that the existence of this type of diet was a major factor in the oxalate stone wave which occurred in Eastern Europe following World War I. Again in World War II, Black (1945) attributed the high incidence of renal colic and hæmaturia amongst British troops in India to hyperoxaluria arising from the ingestion of oxalate-containing foods.

In most of these earlier investigations the existence of hyperoxaluria was inferred from the finding of numerous calcium oxalate crystals in the urine, or from the presence of oxalosis. These are not very sensitive or reliable criteria and it is only within the last few years that reliable quantitative data have begun to appear.

We have developed a method for estimating oxalic acid in biological material which is sensitive and specific (Hodgkinson and Zarembski, to be published), and this method has been used to determine the urinary excretion of oxalic acid in 120 normal individuals and patients with renal stone. During the period of study both groups received a normal balanced diet containing 900 mg. of calcium and 70 mg. of oxalic acid per day. These quantities were checked by analysis.

The daily excretion of oxalic acid by 39 normal adults ranged from 9·0 to 23·8 mg. per twenty-four hours. This range is smaller than the ranges reported by most earlier workers and this is attributed partly to control of the diet and partly to the greater specificity of the analytical technique. In 80 cases of nephrolithiasis the urinary excretion of oxalic acid ranged from 3·0 to 230 mg. per twenty-four hours, but the majority of values were within the normal range. For any one individual the day to day variations were small.

The excretion of oxalic acid in relation to type of stone is shown in Table I.

TABLE I.—RELATIONSHIP BETWEEN OXALIC ACID EXCRETION AND COMPOSITION OF STONE

| Group | Number of individuals | Oxalic acid ($mg. (COOH)_2$ per 24 hours) Range | Mean |
|---|---|---|---|
| Normal individuals | 39 | 9·0 to 23·8 | 17·0 |
| Patients with: | | | |
| I. Calcium phosphate stones | 3 | 8·1 to 27·4 | 16·7 |
| II. Mixed oxalate-phosphate stones | 5 | 15·7 to 22·6 | 18·8 |
| III. Calcium oxalate stones | 13 | 10·5 to 47·1* | 23·5 |

*One additional case had a value of 230 mg. per twenty-four hours.

It is concluded that the urinary excretion of oxalic acid is within normal limits in the majority of patients with nephrolithiasis. A few patients with calcium oxalate stones excrete increased quantities of oxalic acid, but marked hyperoxaluria appears to be rare.

Only one case of marked hyperoxaluria was found in this series. This patient is a man aged 32 with a history of recurrent bilateral calcium oxalate stone starting at the age of 8. In 1955 a right lower polar partial nephrectomy was performed and histological examination of the tissue removed showed the presence of intra-renal calcification with depositions of crystals in colloid casts in the convoluted tubules. Under polarized light the crystals were seen to be birefringent. Under high power magnification some of the crystals showed the typical envelope shape of the calcium oxalate dihydrate crystal. Renal calcification has now advanced to the stage where it is demonstrable radiologically, but there is no evidence of generalized oxalosis. The patient has a recurrent urinary infection which is resistant to antibiotics and his renal function is appreciably impaired (urea clearance, 37% of average normal). There is no evidence of renal tubular acidosis or hyperparathyroidism and no detectable biochemical abnormality except hyperoxaluria and some elevation of the nitrogenous constituents of the blood (urea 51 mg.%; creatinine 3·2 mg.%; uric acid 6 to 9 mg.%). The blood oxalic acid level appears to be normal (1·2 to 1·5 mg.%). Urine pH and urine ammonia, titratable acidity, and amino acids were all within normal limits. No evidence of kidney disease could be found in any of the patient's blood relations.

Approximately 15 cases of recurrent calcium oxalate nephrolithiasis with calcium oxalate nephrocalcinosis have been reported, but the urinary excretion of oxalic acid has been measured in only 5 of these cases. 2 of these cases were described by Archer *et al.* (1958) who suggest the term "Primary hyperoxaluria" to describe the condition. These authors consider that the hyperoxaluria is not due to excessive intestinal absorption of oxalate nor to a low renal threshold for this substance. They suggest that at least part of the urinary oxalate is derived from glycine since administration of glycine to their patients resulted in an increase in urinary oxalate. The increase was, however, small and attempts to reduce the urinary oxalate by reducing the availability of glycine met with only limited success. Aponte and Fetter (1954) observed raised blood uric acid levels in 3 cases of primary hyperoxaluria and considered that this could not be explained entirely on the basis of renal insufficiency. They suggested that the hyperoxaluria is associated with a defect in the metabolism of purines or pyrimidines. We tested this hypothesis by placing our patient on high and low purine diets. On the low purine diet the patient excreted approximately 200 mg. of oxalic acid per day. After two days on the high purine diet excretion increased to over 300 mg. per day. These results support the view that hyperoxaluria may be due to a defect in the metabolism of purines or pyrimidines, and further investigations are in progress.

The author wishes to thank Professor L. N. Pyrah and Dr. C. K. Anderson for permission to use some of their clinical and pathological data, and Mr. P. M. Zarembski for technical assistance.

## REFERENCES

APONTE, G. E., and FETTER, T. R. (1954) *Amer. J. clin. Path.*, **24**, 1363.
ARCHER, H. E., DORMER, A. E., SCOWEN, E. F., and WATTS, R. W. E. (1958) *Brit. med. J.*, i, 175.
BLACK, J. M. (1945) *Brit. med. J.*, i, 590.
GROSSMANN, W. (1938) *Brit. J. Urol.*, **10**, 46.

## BOOKS RECEIVED FOR REVIEW

**Altman (P. L.), Gibson (J. F., Jr.), and Wang (C. C.).** Handbook of respiration. Eds:. D. S. Dittmer and R. M. Grebe. pp. xv + 403. Philadelphia and London: Saunders. 52s. 6d. 1958.

**British National Formulary 1957.** First amendment 1958. pp. 11. London: Pharmaceutical Press. 8d. 1958.

**Code (C. F.), *et al.*** An atlas of esophageal motility in health and disease. pp. ix + 134. Oxford: Blackwell. 63s. 1958.

**Connell (P. H.).** Amphetamine psychosis. Maudsley Monograph No. 5. pp. 133. London: Chapman and Hall. 21s. 1958.

**Cope (Sir Zachary).** Florence Nightingale and the doctors. pp. ix + 164. London: Museum Press. 21s. 1958.

**Davidson (Sir Stanley),** ed. The principles and practice of medicine. 4th ed. pp. xi + 1067. Edinburgh and London: Livingstone. 35s. 1958.

**Dunphy (J. E.),** and **Botsford (T. W.).** Physical examination of the surgical patient. 2nd ed. pp. xv + 375. Philadelphia and London: Saunders. 56s. 1958.

**Flint (T., Jr.).** Emergency treatment and management. 2nd ed. pp. xvii + 539. Philadelphia and London: Saunders. 56s. 1958.

**Gervis (W. H.).** Orthopædics in general practice. Is it rheumatism, Doctor? pp. x + 120. London: Heinemann. 10s. 6d. 1958.

**Gillis (L.),** ed. Modern trends in surgical materials. pp. xi + 266 + 9. London: Butterworth. 72s. 6d. 1958.

**Harvey (B.),** and **Murray (R.).** Industrial health technology. pp. xiii + 337. London: Butterworth. 45s. 1958.

**Harvey (W.).** The circulation of the blood. Trans. K. J. Franklin. pp. xxiii + 184. Oxford: Blackwell. 22s. 6d. 1958.

**Jackson (R.).** The cervical syndrome. 2nd edit. pp. viii + 197. Oxford: Blackwell. 50s. 1958.

**Licht (S.),** ed. Therapeutic exercise. pp. xiv + 893. New Haven, Conn.: Elizabeth Licht. $.16.00. 1958.

**Menninger (K. A.).** Theory of psychoanalytic technique. pp. xvi + 206. London: Imago. 25s. 1958.

**Oliver (L.),** ed. Basic surgery. pp. xvi + 1360. London: Lewis. £6 6s. 1958.

**Rosenheim (M. L.),** and **Moulton (R.),** eds. Sensitivity reactions to drugs. A symposium organized by the C.I.O.M.S. pp. x + 237. Oxford: Blackwell. 35s. 1958.

**Smart (G. A.),** ed. Metabolic disturbances in clinical medicine. pp. vii + 358. London: Churchill. 45s. 1958.

**Studies on Fertility 1957.** Vol. IX: Proceedings of the Society for the Study of Fertility. pp. x + 169. Oxford: Blackwell. 25s. 1958.

**Veall (N.),** and **Vetter (H.).** Radioisotope techniques in clinical research and diagnosis. pp. xii + 417. London: Butterworth. 50s. 1958.

**Willis (R. A.).** The borderland of embryology and pathology. pp. ix + 627 + [illegible]. London: Butterworth. 90s. 1958.

**Wood (I. J.),** and **Taft (L. I.).** Diffuse lesions of the stomach. pp. x + 86. London: Arnold. 24s. 1958.

## BOOK REVIEWS

**A Manual on Cardiac Resuscitation.** 2nd ed. By Robert M. Hosler, M.D., F.A.C.S. (Pp. xx + 208; illustrated. 42s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

The sudden call, by anæsthetist or surgeon attending to a patient on the operating table, that the heart has ceased to beat, strikes awe into the small band that help at the operation, in that their experience has shown that it usually ceases for good. Thus, to restore the heart beat has proved so disappointing a task in the past that suggestions to improve the methods practised in cardiac resuscitation are welcome. This small manual contains such suggestions to overcome cardiac arrest whenever it is met.

The primary aim of resuscitation is to provide adequate oxygenated blood to vital tissues until the heart beat is satisfactorily restored. The upper centres of the brain are the most vulnerable to the lack of oxygen and these suffer irreversible damage if anoxia is prolonged for upwards of four minutes; the next in order of vulnerability are the adrenal bodies and subsequently the kidneys and the liver, followed by the basal ganglia which can survive for up to thirty minutes. To ensure an adequate supply of oxygen to these several stations needs an adequate supply of oxygen in the lungs with efficient elimination of carbon dioxide, sufficient hæmoglobin to transport the oxygen, and a beating heart to propel the oxygenated hæmoglobin to the various organs in order that they may remain viable.

The treatment of cardiac arrest should start with prevention, so that attention should be paid to correcting anæmia if present, premedication with morphine and atropine, correct positioning of the patient on the operating table, and especially the provision of a free air passage to the lungs, for inhalation of mucus or vomitus is the commonest single cause of cardiac arrest.

Once the diagnosis of cardiac arrest has been made no attempt at artificial respiration by compressing the thoracic cage should be made, nor should adrenaline be injected through the chest wall into the heart, or any other kind of intramuscular or intravenous medication. Both anæsthetist and surgeon should immediately embark on their respective urgent tasks. The anæsthetist should introduce an intratracheal catheter and inflate and deflate the lungs adequately by compression of a rubber bag filled with 100% oxygen; this is the foundation of success. The surgeon opens the chest through a transverse incision in the left fifth intercostal space when the heart is lifted up and pressed against the sternum when massage is commenced. Soon the pericardium is opened and massage continued with the heart grasped in the hand. It is then necessary to ascertain whether the condition is one of cardiac standstill or ventricular fibrillation. If the former state prevails and the heart does not resume its rhythmic beat on adequate massage, 5 c.c. of 1 : 10,000 adrenaline solution should be introduced into the right ventricle and massage continued. If ventricular fibrillation is present, the heart is massaged till pink, when the electrodes of the defibrillator are quickly and accurately applied, taking care to disconnect the electrocardiograph before introducing the shock. If necessary 4 c.c. of 1% procaine are introduced into the right ventricle before resuming cardiac massage and repeating the shock from the defibrillator.

This book, expensive as it is, should be in the hand of every anæsthetist and surgeon.

**Circulation. Proceedings of the Harvey Tercentenary Congress.** Ed.: John McMichael, M.D., F.R.C.P., F.R.S. (Pp. xxiii + 503; illustrated. 50s.) Oxford: Blackwell Scientific Publications. 1958.

By general consent the Harvey Tercentenary Congress, held last year under the presidency of Mr. Dickson Wright, was an unqualified success. Owing to the introduction of many new methods of investigation, the time had become ripe for a symposium of our knowledge on the circulation considered from the historical, anatomical, physiological, medical and surgical points of view. The papers, given by a very distinguished group of investigators from all parts of the world, were throughout of a high order, and the transatlantic radio-telephonic discussion was unique.

Professor McMichael has skilfully edited the proceedings and the result is a well-produced and well-illustrated volume of almost 500 pages. It is not a book to be reviewed but to be read, or at least to be on the doctor's shelves ready for constant reference.

How insistently does this book send one's thought back to that wonderful passage in the *De Motu Cordis* where Harvey gave his reasons for publication. As Professor Franklin translates it the passage runs—"that others, given this lead, and relying on more productive talents, may find an opportunity to carry out the task more accurately and to investigate more skilfully". Though of course Harvey was too modest, we, at least, should cut out that thrice repeated "more".

**Rehabilitation after Illness and Accident.** Eds.: Thomas M. Ling, M.D., M.R.C.P., and C. J. S. O'Malley, C.B.E., M.B. (Pp. vii + 119. 12s. 6d.) London: Bailière, Tindall and Cox. 1958.

This small book edited by Dr. Ling and the late Group Captain O'Malley, provides a series of essays dealing with different aspects of rehabilitation and is well balanced.

The contributors have all been associated with St. Thomas's Hospital at some time, and in different spheres of medicine have achieved leading positions. It is particularly gratifying to find such interest shown in rehabilitation by specialists varying from Mr. Harvey Jackson as a neurological surgeon to Professor Lloyd Davies as a professor of social medicine in the University of Malaya.

It would be difficult to comment on which chapters are the most interesting, but the accounts of rehabilitation in general medicine by Dr. John Richardson and on rehabilitation on chest disorders by Dr. John Anderson, made a particular appeal to the reviewer.

**Collected Papers of the Mayo Clinic and the Mayo Foundation.** Vol. 49. 1957. (Pp. xiv + 827; illustrated. 91s.) Philadelphia and London: W. B. Saunders Co. 1958.

The regular appearance every year of a large volume of collected papers of high quality from the Mayo Clinic continues to be one of the minor wonders of medicine. As usual, the wide variety of subjects discussed renders a detailed review impossible. Striking features of the present volume are the series of papers on œsophageal motility studies in disorders of the œsophagus; an analysis of 99 cases of post-bulbar duodenal ulcer; the statement that roentgen therapy is "the most important adjunct in the treatment of patients with regional ileitis"; the analysis of the enormous experience of the clinic in the cytology of uterine cervical smears; and, of course, the series of papers by Kirklin and his associates on their experiences with an extra-corporeal circulation in heart surgery.

One's main regret on reading the volume is at the national self-sufficiency that it, like so much present-day American medical writing, shows. Thus, they manage to discuss the ætiology of Raynaud's disease without mentioning Thomas Lewis; keratoacanthoma without mentioning MacCormac and Scarff; modern operations for varicose veins without mentioning Cockett; and Hashimoto's thyroiditis without mentioning the work of Hudson, Doniach and Roitt. Moreover, in reporting 5 cases of parotidectomy for chronic or recurrent sialadenitis, it is not true to say that previously in this condition "surgical removal of the diseased gland has been almost universally avoided".

Finally, might a plea be made that the scientific value of the volumes would be strengthened by the omission of the long lists of papers "By Title and Reference Only", and by the use of the resulting space for bibliographies for the articles published.

**Fractures and Dislocations.** By George Perkins, M.C., M.Ch., F.R.C.S. (Pp. viii + 363; illustrated. 57s. 6d.) University of London: The Athlone Press. 1958.

Throughout his life Mr. Perkins has been an individualist and a thinker often many years in advance of his times. He has now reached an age when he is having the satisfaction of seeing generally accepted ideas and methods which he taught us long ago and which were at that time considered pure heresy. It is hard to know whether this book was written for students or for his contemporaries (we suspect the latter) but there is no question of the benefit all will reap from its study. Throughout, it is direct, lucid and practical and, as we have come to expect from the author, is frequently illumined with pithy dicta which stick in the memory. The clarity of the introductory chapters could scarcely be surpassed. Although there are a number of points and not a few major theses with which the reader may disagree, this book is a really valuable one which no orthopædic surgeon should fail to read, particularly if he is a teacher. Our only major criticism involves the chapter on head injuries, which is too superficial to be of value and in these days is surely better left to the neurosurgeon.

**Lumbar Disc Lesions. Pathogenesis and Treatment of Low Back Pain and Sciatica.** By J. R. Armstrong, M.D., M.Ch., F.R.C.S. 2nd ed. (Pp. xii+244; illustrated. 45s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

Mr. Armstrong's book is already sufficiently well known to need no introduction, and that a second edition should appear within six years of the first is evidence not only of the author's success in his purpose but of the constant and indeed increasing interest of doctor and patient alike in this most difficult subject. One might argue, probably truthfully, that an enlarging literature on a subject is no proof of greater knowledge, but this book presents and assesses the advances of the last few years with sound and restrained judgment, and can be recommended whole-heartedly to general practitioner and orthopædic surgeon alike.

**Die Infektionskrankheiten des Menschen und ihre Erreger.** Eds.: Prof. Dr. A. Grumbach and Prof. Dr. W. Kikuth. (2 vols. Pp. xl + 1702; illustrated. DM. 198.) Stuttgart: Georg Thieme. 1958.

This comprehensive two-volume work covers the whole field of the infectious diseases known to be caused by bacteria, rickettsia, viruses, fungi, protozoa and some helminths. Its first quarter is devoted mainly to general questions: the characteristics of the various parasites, their relationship to their host and to general problems of epidemiology. The remainder, and larger section of the text takes up separately and in detail the manifold aspects of each disease, its clinical features, epidemiology, ætiology, diagnosis, therapy and, when such is possible, its prophylactic prevention. The completeness of the treatment may be judged from the fact that the treatise is roughly a million words in length.

Much of the value of such a book in English-speaking countries depends on its readability and the comprehensiveness and modernity of its references. As regards the first, it may be said that the style of almost all the contributors is clear, the sentences reasonably short and the technical vocabulary approximating to current international usage. The second requirement is fully met. From a random selection of more than a hundred of the many thousand references in different parts of the book, it was found that about one-third came each from British and American, and one-quarter from German publications. About three-quarters of the references have appeared during the past twenty years.

The book is warmly to be commended as a careful survey by a distinguished group of authors of the many aspects of the infectious diseases. It has been carried out in a much more detailed way than in any present-day work in the English language.

**The Interference Microscope in Biological Research.** By Arthur J. Hale, M.B., Ch.B., Ph.D. (Pp. xi + 114; illustrated. 20s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

The aim of this book is to describe the basic principles, instruments and techniques of interference microscopy in terms that are acceptable to both physicist and biologist. There is perhaps too big a jump between the end of Chapter 1 on "The Physical Basis of Interferometry" and the beginning of Chapter 2 on "Types of Interference Microscope" for this aim to have been achieved with complete success; an intermediate chapter giving an introductory explanation of the functions of the interference microscope would have been advantageous. The book does, however, contain much useful information expressed in a concise and clear style with some very effective diagrams and photographs. At 20s. the price of the book is very reasonable, for the quality of the publication is good.

**Sir Charles Bell; His Life and Times.** By Sir Gordon Gordon-Taylor, K.B.E., C.B., F.R.C.S., and E. W. Walls, M.D., Ch.B., B.Sc., F.R.S.(Ed.). (Pp. xii + 288; illustrated. 42s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

This book is a splendid addition to Messrs. Livingstone's series of medical biographies. There have been many accounts of Sir Charles Bell, anatomist, physiologist, surgeon and artist, but none can have portrayed his character and achievements better. The authors, being themselves distinguished Middlesex men, have no doubt found the task a labour of love. The book's especial merit lies in the picture it paints of life and events in the late eighteenth and early nineteenth centuries; the days of Wellington's campaigns and Waterloo, of the Resurrectionists and the private Anatomy Schools.

This biography is delightfully written, copiously illustrated and attractively produced, it should find a place on the shelves of every medical library.

**Bibliography of International Congresses of Medical Sciences.** Edited by W. J. Bishop under the auspices of the C.I.O.M.S. (Pp. xxii + 238. 25s.) Oxford: Blackwell Scientific Publications. 1958.

Of all the varieties of references quoted, few can have caused more exasperated searching of indexes and catalogues than the reference to some paper of an international congress.

Mr. Bishop's admirable work is an inestimable boon both for its guidance to the existence of published records and for its elimination of those bibliographical "ghosts"—anticipatory references to congresses which never met, or to transactions said to be "in the press," but which never got out of it.

In a characteristically modest foreword, Mr. Bishop sets out the scope of the list and if evidence were needed of the great pains which have been taken in its compilation a reading between the lines of that short statement of scope would give it.

The list itself calls for no comment beyond the compiler's own, that he will be glad to hear of additions and corrections. Any that may be supplied will surely be tributes to the excellence of the original list which has prompted their recording, not reproaches for their omission. The model index fittingly complements the list and the provision of alternative subject titles in English and French should be a great help in its universal use.

There are also English and French versions of the Introduction. That should be read, not only for its comments on the scope and use of the list, but also for its own interest in describing the growth of congresses and their publications.

Mr. Bishop gives the fullest credit to earlier work in the same field; and his acknowledgments again remind us of our very great debt to the National Library of Medicine, Washington, for its work and its never-failing generosity.

The book is pleasant to look at, easy to handle and reasonably priced. The publishers are to be congratulated on a piece of book production which is in their best tradition.

**Human Generation.** Conclusions of Burdach, Dollinger, and von Baer. By Arthur William Meyer. (Pp. ix+143; illustrated. 28s.) Stanford University Press. London: Oxford University Press. 1956.

This book includes the translation from the German of the thesis of Burdach, Dollinger, and von Baer on generation, supplying as well their concise biographies. It clearly depicts the slow emergence of the biological truths of generation from early fantasy—a progress that makes highly interesting reading.

Burdach conceived that the cells and veins are negatively charged, the arteries positively, that crystallization characterized embryonic development, that the early fœtus had its linear end positively charged and its global extremity negatively. He afforded a detailed description of an early fœtus and correctly observed that "the amnion turned about the fœtus to form the fœtal skin". Dollinger speculated that women gave form; men, impulse. He held that no man was entirely male, nor woman female. He regarded the uterine blood as the female semen, which mixed with that of the male, and had some unique views of the ovarian function.

Von Baer's biography is both interesting and arouses human sympathy. He first discovered the ovum and gave precise description of the graafian follicle but failed to discover the embryo. Then again unwittingly he was a pioneer of tubal insufflation whose methods and risks he described.

All three were possessed of strong religious conviction and condemned the evolutionary thesis.

**The Medical Annual 1958.** Edited by Sir Henry Tidy, K.B.E., M.A., M.D.Oxon, and R. Milnes Walker, M.S.Lond., F.R.C.S. 76th issue. (Pp. xl+580+23; illustrated. 42s.) Bristol: John Wright & Sons, Ltd. 1958.

A major change in this 76th *Medical Annual* is an alteration in the mode of presentation, so that the reviews by the various contributors are collected together under the appropriate heading rather than being arranged alphabetically. This will be welcomed. The retirement of Sir Henry Tidy is much to be regretted, as this will be the last of twenty-five issues to be edited, from the medical point of view, by him. The whole book is indicative of the vitality of the editors and contributors, and it is characteristic that the changes have been made during Sir Henry's editorship.

The quality of this famous *Annual* has been fully maintained, and in it there is much for everyone.

**Diseases of the Liver and Biliary System.** By Sheila Sherlock, M.D.Edin., F.R.C.P.Lond., M.R.C.P.Edin. 2nd edit. (Pp. xvi+719; illustrated. 57s. 6d.) Oxford: Blackwell Scientific Publications. 1958.

Those who already admire Dr. Sherlock's book will welcome the second edition and seek out the plentiful new material with enthusiasm.

The chapter on jaundice is particularly helpful as the clinical problem of the jaundiced patient is not only frequently encountered, but is at times most testing.

In spite of the introduction of a great deal of new subject matter, the book is not increased in length, and this is indeed a considerable feat.

The reputation of this book will be enhanced by this edition.

**How to Write Scientific and Technical Papers.** By Sam F. Trelease. (Pp. xii+185; illustrated. 26s.) London: Baillière, Tindall and Cox Ltd. 1958.

This little book, which is written and produced in the United States, could usefully find a place on the desk of anybody faced with the task of writing for medical or scientific journals. It contains the answers to most of the questions which authors ask and the practical advice on preparing illustrations, graphs and papers could hardly be bettered. The "puff" on the dust wrapper is unsuited to British readers and might well be replaced by something more in keeping with the book itself. The first paragraph of the author's own preface would be admirable for this purpose.

**Medicine and the Navy, 1200–1900.** Vol. II. 1649–1714. By John J. Keevil, D.S.O., M.A., M.D., M.R.C.S., L.R.C.P., D.T.M.&H. (Pp. 331; illustrated. 40s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

The first volume of this magnificent work was reviewed in our columns (*Proceedings*, 1957, 50, 982) and this, the second volume, fulfils all that was expected of it. Indeed it covers a more fascinating and formative period of naval medicine and the author has warmed to his subject.

It is tragic that Surgeon Commander J. J. Keevil should have died before he was able to complete the whole work which even in its present state is a classic. Let us hope that the Wellcome Trustees will succeed in finding one who can follow in Keevil's footsteps and complete this splendid historical review.

**An Introduction to Surgery.** Edited by David H. Patey, M.S.Lond., F.R.C.S.Eng. (Pp. xi+228; illustrated. 17s. 6d. Students' edition: 9s. 6d.) London: Lloyd-Luke (Medical Books) Ltd. 1958.

This admirable little book, which is obviously intended to fit in the pocket of a medical student when he first embarks on his clinical work, can be recommended unreservedly. Some may doubt whether there is a place for multiple authorship in a book which should be framed in the broadest terms, but if that is so here is the answer. The text is clear and always to the point, the illustrations are simple and very informative and there is a nice blending of practice and theory. The text shows evidence of meticulous correction and preparation.

An interesting feature of this publication is that Messrs. Lloyd-Luke have produced the book in two editions, one in stiff covers at 17s. 6d. and the other bound in paper at 9s. 6d. This is a reply to the friendly challenge contained in an annotation in the *Lancet* last year and there is no doubt that the impecunious student will be indeed grateful to them for this most welcome innovation.

**The Reticulo-Endothelial System in Growth and Tumour Formation.** By Roger Wyburn-Mason, M.A., M.D.Cantab., M.R.C.P.London. (Pp. 206; illustrated. 42s.) London: Henry Kimpton. 1958.

The first part of this monograph (108 pages) is devoted to a historical review of the reticulo-endothelial system and a detailed analysis of the relationships that macrophages bear to other tissue cells and to nerve fibres, both in normal and pathological states. Much of the descriptive matter is derived from the author's own investigations, using vital and supravital staining of human and animal tissues with such dyes as methylene-blue, trypan blue and Janus green.

In the second part of the book, Dr. Wyburn-Mason discusses the functions of the macrophage system and elaborates his thesis that it is ". . . an essential link by which the metabolism of the cells of a tissue is controlled and correlated with the rest of the body by nervous and hormonal mechanisms". He goes on to discuss the abnormal distribution of macrophages in developmental abnormalities and neoplasia.

The book is well written and well produced. The majority of the photomicrographs are of good quality but some are rather unsatisfactory (as the author himself acknowledges in the preface). The presentation of many new and controversial ideas makes this an interesting and stimulating work. It should encourage further investigation into the functions of the reticulo-endothelial system in health and disease.

**Textbook of Surgery.** Edited by Guy Blackburn, M.B.E., M.Chir., F.R.C.S., and Rex Lawrie, M.D., F.R.C.S., M.S., M.R.C.P. (Pp. xii+1122; illustrated. 84s.) Oxford: Blackwell Scientific Publications. 1958.

Textbooks of surgery often suffer from the authors' uncertainty as to whether they should write for undergraduate or postgraduate students. The attempt to write for both is usually unsatisfactory. The present book is expressly designed for the undergraduate. The writing of a textbook of surgery for undergraduates presents special difficulties since surgery is essentially a postgraduate subject; the undergraduate studies surgery chiefly as one important source of the general principles of medicine. He cannot, however, get at these general principles without knowing some details. The main features of this attractively produced volume from the Guy's School are its clear statement of facts, and a simple classificatory style which avoids the staccato. The tone is set by an excellent first chapter by one of the Editors, Mr. Rex Lawrie, who starts with the definition: "Surgery is the study of treatment by operative methods. By this is meant the selection and preparation of patients for operation, details of the operative procedure and post-operative care, and the management of the phases of recovery and rehabilitation until the patient returns to normal activity." The Editors, who between them have written 14 of the 40 chapters, have succeeded in fitting the style and content of their colleagues' contributions into a general pattern.

The reduction of surgical pathology to a minimum, a policy deliberately adopted by the Editors in the successful attempt to avoid making the book too long, naturally has its disadvantages. In places facts stand isolated without explanations. As a result, the student may find the book more useful to answer his "whats" than his "whys". For example, in describing femoral hernia the statements are made that there is "usually no expansile impulse on coughing" and that the sac "tends to spread upwards over the region of the external ring", but without indicating the reasons. Terms are sometimes used without being defined, e.g. "closed loop obstruction", "Miller-Abbot tube". There is, as would be expected from Guy's, an authoritative account of the modern surgery of the heart. But the chapter would be improved for undergraduates by the exclusion of such sentences as "Rarer causes of congenital heart disease are persistent truncus arteriosus, acyanotic Fallot's tetralogy and the members of the Eisenmenger group of heart conditions". In the foreword Sir Russell Brock rightly points out that the perfect textbook will never be written; one can only aim at an unattainable ideal. There are obvious advantages in basing a textbook on one great medical school; a community of outlook is more easily achieved, and individual contributors are more likely to tolerate editorial criticism and revision. The work compares favourably with the standard textbooks, and will clearly become a standard textbook itself.

**External Collimation Detection of Intracranial Neoplasia with Unstable Nuclides.** By G. M. Shy, M.D., M.R.C.P., R. B. Bradley, B.S., and W. B. Matthews, Jr., B.S. (Pp. vii+144; illustrated. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1958.

The availability of fission by-products and induced radioactivity of elements by neutron bombardment or charged particles, via massive accelerators such as the cyclotron, made the utilization of such substances in the detection of neoplasia almost inevitable. In this book, Dr. Shy and his colleagues describe the various scanning devices, collimators, used in association with the intravenous injection of certain isotopes in the diagnosis of cerebral and cerebellar tumours and of other pathological states within the skull such as abscesses, cerebrovascular accidents and vascular malformations.

The physics of the method are discussed in great technical detail and there is a chapter on the selection of isotopes. Since all tissues, particularly muscles, take up these substances in varying concentration the physician must be familiar with the scan of the normal head before scans of patients suffering from pathological processes can be appreciated. There are numerous illustrations of both the normal and the abnormal, and the method is clearly described. At the present time, external collimation detection only approaches in reliability the conventional diagnostic measures, but the book, which is well produced, provides an introduction to a fascinating new technique.

**Woman's Change of Life.** By Isabel Hutton, C.B.E., M.D. (Pp. 124; 6s.) London: William Heinemann Medical Books Ltd. 1958.

This little book has been written by a distinguished woman doctor to help women who are approaching or experiencing the menopause.

It consists mainly of explanation of the various symptoms and bodily changes that can be expected. The subject is dealt with very comprehensively and is pervaded by reassurance and practical common sense—in fact, just what is most needed by an apprehensive woman approaching this event in her life.

It can be strongly recommended as one of the best books of its kind. Many doctors would profit by reading it, since such detailed information is not generally to be found in textbooks of medicine and gynæcology. On the other hand, menopausal complaints are frequently encountered in many branches of medical practice.

**Transactions of the American Ophthalmological Society 1957.** Vol. 55. (Pp. xix+805; illustrated. 144s.) Columbia University Press. London: Oxford University Press. 1958.

The contents of the 55th Volume of the *Transactions of the American Ophthalmological Society* are evidence of a thriving concern. Temporal arteritis, toxoplasmosis, leprosy, viral diseases, Graves' disease, and cerebral meningiomata are some of the general conditions discussed as they affect the eye. In the special sphere, retinal detachment, uveitis, gonioscopy, and corneal changes from exposure to hydroquinone are the subjects of most interesting papers. A historical discussion on the concept of semidecussation of the optic nerves is of particular interest to the British reader because of the part played by Isaac Newton. The second half of the volume contains twelve theses written and submitted by candidates for membership. They are practical in outlook, based sometimes on a large experience and all of high standard. The whole forms a worthy addition to a long and distinguished series.

# Section of Neurology

President—HUGH GARLAND, T.D., M.D., F.R.C.P.

[*October* 2, 1958]

## Endogenous Hypoglycæmia

### PRESIDENT'S ADDRESS

By HUGH GARLAND, T.D., M.D., F.R.C.P.

*The General Infirmary at Leeds*

FOUR hundred years ago Shakespeare attributed to John of Gaunt the epigram "Things sweet to taste prove in digestion sour" (Richard II). This was an astute observation on a type of hypoglycæmia which is only partially understood even now and still little known. Endogenous hypoglycæmia is a condition in which low blood sugar concentrations appear to be the primary cause of symptoms, but I only propose to discuss certain aspects. "Endogenous" is a more accurate term than "spontaneous," since there must always be a reason for the development of hypoglycæmia even if it cannot be fully explained. Despite extensive animal experimentation, clinical observation, and a welter of medical writings, the complete clinical picture—which is the aspect of greatest importance to the neurologist—has not yet been fully assessed. Because of the metabolic limitations which are peculiar to nervous tissue, the protean symptoms of hypoglycæmia fall predominantly into the neuro-psychiatric sphere; but hypoglycæmia is not a simple condition for clinical study nor an easy diagnosis to uphold and prove scientifically. Even in 1958, however, there is little "scientific" proof of many neurological diagnoses, this being especially true of disseminated sclerosis, and the neurological complications of cervical spondylosis and polyarteritis nodosa.

#### PHYSIOLOGY

The activity and existence of the nervous system depend largely on the metabolism of glucose, but neural performance may remain normal despite a wide variation in the concentration of available glucose as determined by peripheral blood sugar measurements. Certain "normal" variations of blood sugar in relation to the fasting or post-prandial state are accepted, but the upper limits are extremely wide, and very high figures, including those of severe diabetes, cannot be related to signs or to symptoms. The significance of low levels is even more dubious; their effects present many unsolved problems, and biochemical hypoglycæmia, like hyperglycæmia, often has no clinical counterpart.

Although any physician would regard certain blood sugar values as normal there are few biochemists prepared to state the normal range. One accepts that if the venous blood sugar is 150 mg.% two hours after a meal the patient is probably suffering from diabetes, but what constitutes an abnormally low level is by no means agreed; the figure of 70 mg.% is not regarded with suspicion, but most would feel that 60 is unusual and 50 abnormal, though the figures vary somewhat according to the method of estimation. There is no constant time-correlation between the clinical state and low blood sugar concentrations, and sometimes no correlation at all. A figure of 25 mg.% was once thought to be incompatible with life, but eleven years ago I saw a patient whose fasting blood sugar level was precisely that figure, who only suffered from occasional attacks of unconsciousness, and who achieved complete symptomatic relief by taking a high-carbohydrate diet (Fig. 1).

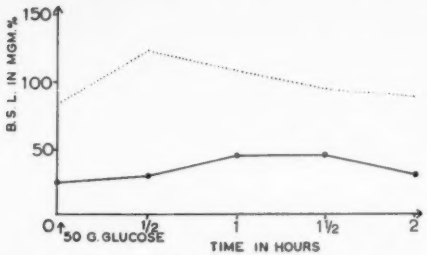



FIG. 1.—Hypoglycæmic fits relieved by high carbohydrate diet. (In this and other illustrations the dotted line is an average normal glucose tolerance curve.)

In children with the rare glycogen-storage disease of von Gierke, which is inherited as a mendelian recessive, the blood sugar is always in the region of 60 mg.% or considerably less, and cannot be raised by injecting adrenaline; but they rarely show any evidence of cerebral dysfunction and are unlikely to come the way of the neurologist. Hyperinsulinism occurs in children, though often with little evidence of hypoglycæmic symptomatology, and blood sugar levels may be extremely low in infancy, especially in babies born of a diabetic mother, where compensatory islet hyperplasia arises to overcome the maternal hyperglycæmia (Farquhar, 1956).

The technique of estimating blood sugar has considerable bearing on the interpretation of figures. Most of my patients were examined in the Leeds General Infirmary where a modification of the Folin-Wu method, using venous blood, has always been used. The glucose-oxidase method, which is specific for glucose, will probably be more widely used in the future, and it may well show figures which are 20 mg.% lower at all levels. The diet taken during the few days preceding a glucose tolerance test is most important and if the carbohydrate intake has been reduced the test becomes completely unreliable (Conn, 1940*a*).

## ÆTIOLOGY

As neurologists, we are concerned with the signs or symptoms which result from hypoglycæmia as opposed to the incidental finding of low blood sugar levels in such disorders as Addison's disease, hypopituitarism, or gross liver damage. Presenting clinical endogenous hypoglycæmia may arise in three main ætiological groups, namely (1) as organic hyperinsulinism which results from the presence of a functioning pancreatic islet-cell tumour, (2) as a complication of gastric surgery, or (3) by predominantly psychological mechanisms. Apart from its therapeutic value, insulin has been used by the malingerer and has sometimes resulted in total pancreatectomy, though as far as I know this particular perversion has not been recorded in Great Britain. Insulin has also been used as a suicidal agent, and once at least in this country in the furtherance of murder (Birkinshaw *et al.*, 1958). Insulin "reactions" in the diabetic and insulin "shock" treatment have been studied for more than a quarter of a century. The effects of exogenous hypoglycæmia do not always mimic the symptoms produced by the endogenous form, and the manifestations of endogenous hypoglycæmia do not always follow the same pattern irrespective of the basic ætiology. Despite common nosological ground, the wide variation in the symptomatology of both exogenous and endogenous hypoglycæmia suggests that low blood sugar levels are not always the only, or even the main, factor.

*Organic hyperinsulinism.*—Though islet tumours, both adenomata and carcinomata (relatively 70% and 30% of proved examples), may well be as old as man himself, the earliest example recorded was in 1902 (Nicholls); and it was not until 1927, in the Mayo Clinic (Wilder *et al.*), that the clinical diagnosis of organic hyperinsulinism was made and upheld at autopsy, nor until 1929 (Howland *et al.*) that the first islet adenoma was successfully removed in Toronto.

The islets of Langerhans contain *alpha* and *beta* cells with both histological and functional differences (Gomori, 1939); the *beta* cells are thought to secrete insulin, while the *alpha* cells produce glucagon, which possibly acts as an anti-insulin substance. The two types of cells can be identified histologically, but unfortunately this technique has rarely been applied to pancreatic tumours so that we cannot be certain whether they consist purely of *beta* cells or *alpha* cells, or both, though it has been known for many years that an islet adenoma may be "functioning" or "not-functioning" as regards the secretion of insulin. As far as I know there is no proved example of an *alpha*-cell tumour producing diabetes,

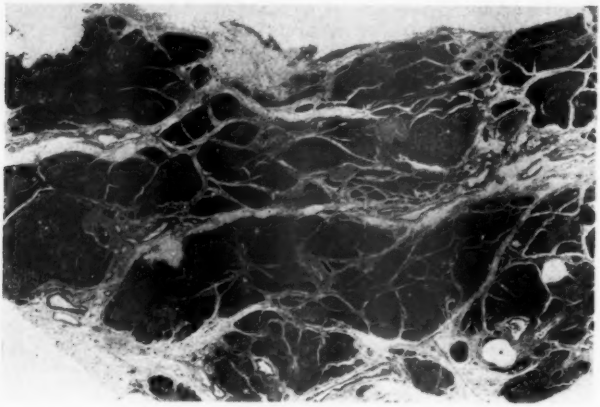
though this would be a theoretical possibility. Similar *alpha* cells are found in the upper three-quarters of the gastric mucosa of the dog (Sutherland and de Duve, 1948) and if this is also true of man it might have the greatest clinical importance.

The precise mechanism whereby insulin secretion is normally controlled is complex. The islets may respond in step with the current blood sugar concentration, but if so there are many proved clinical anomalies. The average secretion of the adult pancreas is thought to be about 40 units per day, though this estimation is based on the results of total pancreatectomy which must also remove a large number of *alpha* cells. Since many organs (and especially the brain) are constantly metabolizing glucose, it is probable that insulin is being continuously produced. We have no idea of the insulin output of an adenoma, but this could be much greater, or smaller, than that of the whole pancreas. Still less do we know what mechanisms govern the secretory function of the adenoma, which may well be autonomous. We do know, however, that the symptoms resulting from adenomatous activity may bear no relationship to the fasting state, or have any temporal association. But there may be a point in the evolution of a functioning adenoma when it provides all the insulin requirements of the body so that activity of the islets is in abeyance; this is suggested by the microscopic degranulation changes which appear in the *beta* cells of the remainder of the pancreas in the presence of an active adenoma, but not if the tumour is inactive (Nerenberg, 1954). Low blood sugar concentrations may return to normal or even reach hyperglycæmic levels within a few minutes of the surgical removal of an adenoma (Garland, 1957*a*) but as far as I know permanent diabetes has never followed this procedure. In clinical assessment, we must also remember that an adenoma may sometimes cease to produce insulin, or that its secretory activity may remain static.

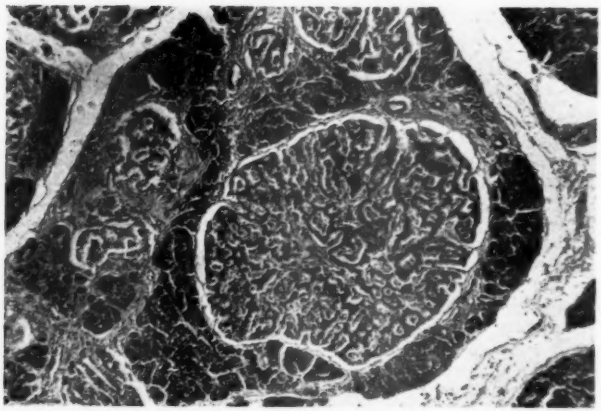
At the time of writing the number of proved examples of organic hyperinsulinism is probably not more than 600 or 700, though 91 were seen in the Mayo Clinic between 1927 and 1953 (Breidahl *et al.*, 1956); but insulin "shock" therapy must have been given millions of times, considering that schizophrenia is the commonest diagnosis made on hospital patients at any given time, that most of these have had insulin therapy over the past twenty-five years, and that such treatment is carried out daily for several weeks. The observed effects of insulin treatment of psychotics show many similarities to organic hyperinsulinism, but also many differences, which may be determined in some way by the schizophrenic make-up. This does not apply, however, to patients suffering from psychoneurotic tension syndromes, in whom an injection of 100 units of soluble insulin is usually not followed by any symptoms.

So many laboratory aids are now available for confirmation of the diagnosis of hyperinsulinism that there can be little excuse for a futile abdominal exploration. Unsatisfactory operations have been not infrequent in the past, for three important reasons: The pancreas may look normal when in fact it is the site of diffuse, microscopic adenomatosis; an adenoma may be deeply buried in the head of the pancreas; and in 12% there are multiple adenomata. The first of these problems calls for an immediate decision at the time of laparotomy; provided the diagnosis has been established beyond reasonable doubt, the surgeon should be asked, if the pancreas appears normal, to remove the caudal half of the organ, which is a relatively easy procedure. I have no doubt that failure to carry out hemi-pancreatectomy is the main reason why the total number of recorded examples of islet adenomatosis only stands at 8 (Garland, 1957*a*). An adenoma in the head of the pancreas or multiple adenomata may still be overlooked but there is no method whereby the pre-operative differentiation between adenoma and adenomatosis can be made. Total pancreatectomy is a formidable operation and multiple explorations are undesirable. Perhaps unnecessary procedures might sometimes be avoided by the use of rapid frozen-section biopsies when the pancreas is macroscopically normal, since recorded examples suggest that adenomatosis, though not involving all the islets, is widespread (Figs. 2A and B). If such a biopsy shows no abnormality the possibility of ectopic adenomata must also be kept in mind; these are as infrequent as adenomatosis but are occasionally found in adjacent structures.

Even when the diagnosis of hyperinsulinism has been adequately confirmed, laparotomy may be undesirable or impossible, and I have known 3 patients in this category. A middle-aged man refused operation. A woman of 75 was considered too old for surgery unless other methods failed, and a child of 4 was thought to be too young. All 3, and others in whom the diagnosis was less certain, responded very well to dietetic treatment. Hyperinsulinism can be controlled wholly or partially by a high-carbohydrate diet, and though the rationale is based on the unproved assumption that the patient is being constantly subjected to an abnormally high secretion of insulin which may be counterbalanced by the excessive ingestion of carbohydrate, the clinical results are often conclusive. There is great confusion about the dietetic treatment of hypoglycæmia. Conn has written prolifically on this subject over the past twenty years. In 1940 he described the value of a



A



B

FIG. 2.—A, The pancreas shows numerous adenomatous islets of variable size. (Hæmatoxylin and eosin × 6 approx.) B. Adenomatous islets of Langerhans. The largest is almost completely surrounded by exocrine lobules which are small, dark and compact. (Hæmatoxylin and eosin × 40.)

high-carbohydrate diet in organic hyperinsulinism, and of a high-fat, high-protein and low-carbohydrate intake in the treatment of "functional" hypoglycæmia (Conn, 1940*b*). But many writers since then have used the latter diet in treating organic hyperinsulinism without explanation (Cohen, 1950; Breidahl *et al.*, 1956). My own experience supports Conn's views. The advantage of a high-carbohydrate diet, apart from the relief of symptoms, is its cheapness; the disadvantage is the resulting obesity, especially if surgical intervention becomes unavoidable. It must be emphasized, however, that although the continuous dietetic treatment of hypoglycæmia depends on the ætiology, immediate relief of symptoms may be obtained by taking glucose.

How is the diagnosis of hyperinsulinism to be established? The appropriate investigations will obviously not be carried out unless the diagnosis is suspected on the basis of the clinical history, and occasionally on the physical signs. Unfortunately all the diagnostic aids have rarely been applied to proved examples, and for this reason the significance of the various investigations is not clearly defined. Whipple's triad (Whipple, 1938) for the diagnosis of organic hyperinsulinism was a valuable clinical advance; it stated that the fasting blood sugar level should be persistently low, that attacks of some kind, obviously resulting from

disordered cerebral function, occurred in the fasting state, and that these attacks could be rapidly relieved by taking glucose. Although this is still a useful guide, it is not always strictly true, for my patient (Garland, 1957*a*), with adenomatosis, who had suffered from attacks of automatism with amnesia for several years, had never had symptoms in the fasting state, and had repeated fasting blood sugar concentrations of 60 mg.% or more. During a glucose tolerance test on this patient (Fig. 3) the peripheral blood sugar was maintained steadily at 50 mg.% and it was not until the end of four hours that symptoms appeared, and then rapidly. Many test-tube-minded physicians will be shocked at the serious and authoritative suggestion that the glucose tolerance test plays no part in the diagnosis of hyperinsulinism (Breidahl *et al.*, 1956; Richardson and Hill, 1957), but this heresy has considerable practical backing. In many patients with proved hyperinsulinism (including some of my own) a glucose tolerance test has been normal. More often the fasting blood sugar level is obviously low and the curve tends to be flat or it may even be inverted; but Fig. 4 shows a low fasting level with return to normal values in a patient from whom an islet adenoma was later removed. Fig. 5 is the glucose tolerance test carried out

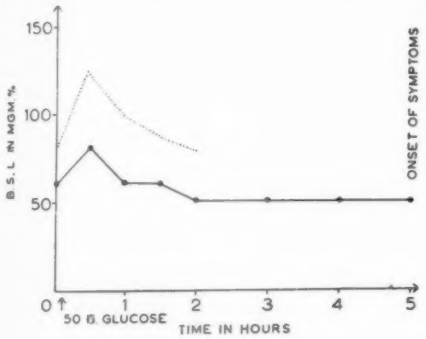



FIG. 3.—Glucose tolerance test in proved islet adenomatosis.

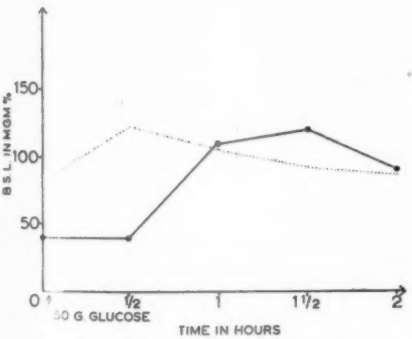



FIG. 4.—Glucose tolerance test in proved islet adenoma.

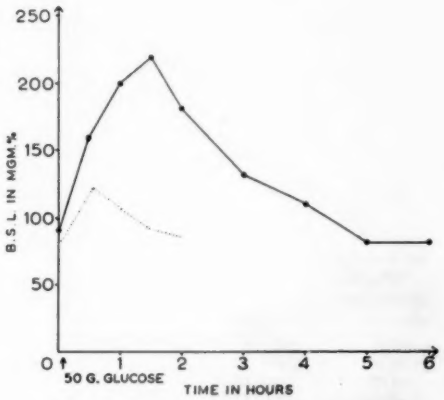



FIG. 5.—Glucose tolerance test in a patient proved to have hpyoglycæmic attacks.

two days after severe neurological symptoms in an old lady. Many physicians would reject the possibility of hypoglycæmia on this particular test, but in a later attack she was found to have a blood sugar level of 40 mg.%, and her symptoms were immediately reversed by adrenaline. Since that episode, six years ago, she has taken a high-carbohydrate diet and has remained symptom-free. Random fasting blood sugar estimations are not always helpful, but abnormalities may be aggravated by twenty-four to seventy-two hours' starvation, especially if this be followed by vigorous exertion, though such investigations

are not likely to be of much value unless they precipitate symptoms of the appropriate kind. Even when the patient is suffering from hypoglycæmic symptoms there is no constant relationship between the concentration of the peripheral blood sugar and cerebral function. The finding of a level of 50 mg.% or less is highly suggestive of a hypoglycæmic ætiology, and 30 mg.% is almost diagnostic of organic hyperinsulinism, though a normal level when symptoms appear by no means excludes the diagnosis. The opportunities for such tests rarely occur, but despite all the difficulties many patients have had successful surgical treatment on the basis of blood sugar estimations alone.

If symptoms result intermittently from hyperinsulinism they might be precipitated by the injection of insulin. This has been proved, as little as 5 units in the fasting state reproducing the original symptoms in a patient from whom an islet adenoma was later removed (Fraser *et al.*, 1939). Moreover, observations of the greatest importance in relation to post-operative and psychosomatic hypoglycæmia were made by this method in the same patient; time-correlation of blood sugar concentration with the clinical state showed that if the fall was rapid symptoms occurred at about 70 mg.%, although much lower levels were not associated with symptoms if the fall was slow. Because the manifestations of hypoglycæmia may be not only unpleasant but also sinister, and because hypoglycæmic coma may quickly become irreversible, such a diagnostic test should only be carried out under the strictest supervision. But symptoms produced by insulin are rapidly relieved in the early stages by glucose, and the giving of insulin to such patients is no more ethically questionable than starvation with or without exercise. I feel, therefore, that we should always apply the full diagnostic battery before any patient is subjected to surgical procedures.

Other methods of investigation include the intravenous glucose tolerance test (which I have never used) and the "loaded" oral glucose tolerance test. Personal experience of the latter, using 300 grams of glucose, has not been helpful because the patients frequently vomit (which happens occasionally with the usual dose). There is little proof that more than 50 grams is necessary to produce an adequate hyperglycæmic stimulus.

Bio-assay of the plasma insulin concentration by a complex technique using rat diaphragm has shown high insulin levels in the presence of an adenoma, and a rapid fall to normal after its removal. This method has only been used in a few centres (Vallance-Owen and Hurlock, 1954) and its complete reliability may not yet be proved beyond doubt. Perhaps a more simple assay will be the estimation of insulin-like activity using rat adipose tissue (Martin *et al.*, 1958).

Electro-encephalography (EEG) may play a diagnostic role; it has been both totally disparaged (Breidahl *et al.*, 1956) and strongly advocated (Laidlaw and Rab, 1957). The EEG changes in hypoglycæmia are non-specific, only reflecting a depression of cerebral metabolism, and they must be considered in relation to both symptoms and blood sugar concentrations at the time of recording. Increasing hypoglycæmia causes disappearance of the *alpha* rhythm and later *theta* and *delta* waves appear, though there is no critical level at which these changes invariably occur. The clinical picture can be more closely correlated with the simultaneous electrical changes than with the simultaneous blood sugar level (Wyke, 1952). EEG changes mirror the clinical state or perhaps anticipate it (Brazier *et al.*, 1944), just as biochemical hypoglycæmia may precede considerably the appearance of clinical manifestations, although both may be unassociated with symptoms. EEG abnormalities in hypoglycæmia may be provoked by overbreathing and may be reversed by giving oral glucose even though the patient is making no complaints, and this finding may be very important.

Whether hypoglycæmic symptoms arise "spontaneously" or from cold-blooded iatrogenesis, the most valuable diagnostic test must be their reversal by glucose, the route depending on the patient's state of consciousness. They may also be reversed by adrenaline or ephedrine, but neither is as reliable as glucose and should not be used unless the patient is in coma, when the administration of nasal or intravenous glucose may be impracticable.

*Hypoglycæmia complicating gastric surgery.*—Post-prandial symptoms resulting from gastric operations have been known for more than forty years. In the earlier part of the century the common surgical procedure of gastro-enterostomy was always potentially reversible. More recently there have been variable waves of enthusiasm for the irreversible procedures of gastrectomy (partial or total) and vagotomy. These operations may also determine hypoglycæmia with clinical manifestations which fall into two groups with both clinical and ætiological differences. In the first group the patient feels faint within minutes of taking food because a meal of high-carbohydrate content, which is hurried into the jejunum, produces a sharp fall in blood volume by osmotic mechanisms. This is rapidly reversed, but is closely related to the appearance of symptoms and ECG changes, and constitutes the "early dumping syndrome" (Medwid *et al.*, 1956). Such episodes are

largely abolished by reducing the carbohydrate intake, and taking meals of high-fat and high-protein content. In the second group, symptoms, which may be serious, appear one to two hours after food. The mechanism is not yet fully understood, though we know that after gastric operations, and particularly gastrectomy, there is sometimes a permanent disturbance of glucose metabolism. In these patients the glucose tolerance test shows a reactive type of curve; the fasting blood sugar level is normal but there is a rapid rise to an abnormally high figure, which is followed by a rapid fall either to normal or to hypoglycæmic levels, the lowest figure I have seen being 30 mg.%. If symptoms arise, they may be determined by low blood sugar concentrations or, perhaps more often, by the rapidity of the fall, which may be 100 mg.% or more in half an hour. The reactive type of glucose tolerance curve has usually been thought to result from the sudden absorption of a large amount of glucose which stimulates excessive secretion of insulin by the pancreatic islets. Such a view is supported by the time-lag between taking food and the appearance of symptoms, and by the undoubted improvement which follows the reduction of carbohydrate intake. But this theory does not explain why these syndromes only occur in a small proportion of patients, and other factors must be considered. There are presumably no important mechanical differences between one vagotomy and another, though there are various methods of performing gastro-enterostomy, and still more variability in the technique of gastrectomy. Symptoms are more likely to arise in people with a pre-operative neurotic make-up, and there are many points of similarity between this group and the psychosomatic type of hypoglycæmia. But another factor which has not yet been assessed may be all-important—namely the possible removal during gastrectomy of *alpha* cells which may determine a decreased secretion of glucagon. None of these theories, except perhaps that of psychogenesis, accounts for the fact that there is almost invariably an interval before the appearance of symptoms, which may be as long as thirteen years. A sudden dietary indiscretion is unlikely to be the explanation of symptoms appearing after this latent interval, though I have seen two patients in whom hypoglycæmic syndromes were apparently precipitated in the fasting state by alcohol. One of these had had a subtotal gastrectomy ten years previously and on three occasions alcohol rapidly produced symptoms, once in the form of prolonged coma. The other, thirteen years after gastro-enterostomy, had a long phase of automatism with patchy amnesia. Both showed glucose tolerance curves of the reactive type, with hypoglycæmic levels; the second had taken only a moderate amount of alcohol, and the first a homœopathic quantity—judged by anybody's standards. I have tried to reproduce symptoms in this way, to the satisfaction of the patient but without the advancement of clinical science, though there is experimental evidence that alcohol can depress cerebral metabolism *in vivo* (Thompson and King, 1957).

Unfortunately there have been few extensive glucose tolerance studies after gastric operations, and I am not familiar with any investigation of glucose metabolism before and after operation. In the largest series, from Glasgow (Muir, 1949), tests were carried out on 86 patients after subtotal gastrectomy. Of these, 52 were normal; many of the others showed reactive curves sometimes reaching 300 mg.% within an hour. 6 patients showed hypoglycæmic symptoms two hours after food, the latent period varying from three to seventeen months. I have recently done glucose tolerance tests before and after partial gastrectomy on 8 patients; there had been no change in the shape of the curve and only a slight general lowering of blood sugar levels after operation (though 50 mg.% appeared several times) with one striking exception (Fig. 6): this remarkable post-operative glucose tolerance test was carried out four months after a partial gastrectomy, when the patient was doing heavy work, on a normal diet, and entirely free from symptoms.

Establishing the diagnosis is more difficult in the post-operative group than in the first; indeed these syndromes have frequently been overlooked because neither physician nor surgeon has considered that transient neuro-psychiatric disturbances could be related to a previous gastric operation. When it is thought that symptoms may be of this ætiology, no matter how remote the operation, a prolonged glucose tolerance test (lasting six hours) may be suggestive. Personal attempts to precipitate symptoms in such patients by small doses of insulin have failed. As in organic hyperinsulinism, symptoms can be quickly relieved by taking glucose at an early stage, or by the injection of adrenaline, and the value of giving the patient a low-carbohydrate, high-fat, high-protein diet as a therapeutic test is, in my experience, unquestionable.

*Psychosomatic hypoglycæmia.*—The term "psychosomatic" is preferable to "functional" or "nervous" hypoglycæmia for obvious reasons. Some observers consider psychogenesis to be much the commonest cause of endogenous hypoglycæmia (Conn and Seltzer, 1955) but this has not been my own experience. The diagnosis is even more difficult to confirm than in the first two groups and is usually only made when a patient with a number of neurotic symptoms describes transient events which have a remarkably "organic" stamp—

for example, sudden attacks of unconsciousness which are obviously neither syncopal nor hysterical. Again the prolonged glucose tolerance test may be helpful, as well as the therapeutic trial of a high-fat, high-protein diet, or the rapid reversal of symptoms by glucose.

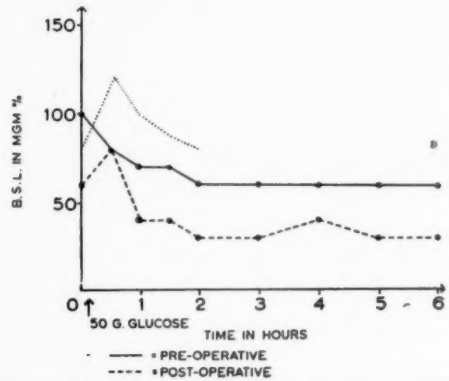



FIG. 6.—Effect on glucose tolerance test of partial gastrectomy but without hypoglycæmic symptoms.

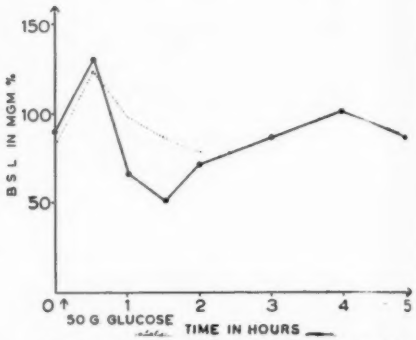



FIG. 7.—Psychosomatic hypoglycæmia with oscillating levels.

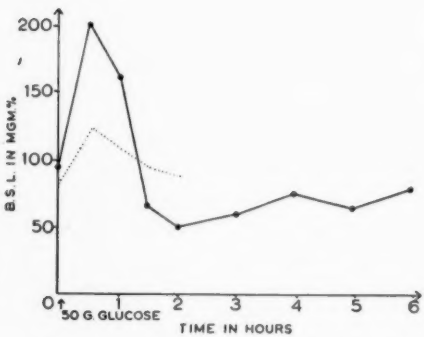



FIG. 8.—Psychosomatic hypoglycæmia showing a reactive curve followed by oscillating levels.

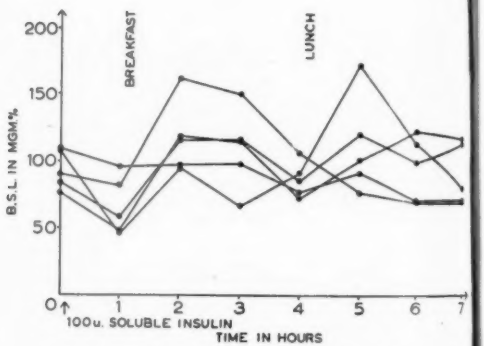



FIG. 9.—Blood sugar levels in normal subjects following 100 units soluble insulin.

The mechanism is thought to simulate that of the post-operative group, gastro-intestinal hurry (which can undoubtedly be determined by psychogenesis) resulting in rapid and excessive absorption of glucose. In some of these patients there is a reactive glucose tolerance curve like that seen after gastric operations, but often the usual smooth rise and fall is changed into a series of oscillations during which unusually low figures may be reached; in others oscillating levels may follow an initial reactive peak (Figs. 7 and 8).

In the treatment of psychogenic tension states, provided normal meals are taken, most patients will tolerate an injection of 100 units of soluble insulin on waking, and will develop no symptoms other than increased appetite and sweating. Of 45 patients treated by this method only 2 were unable to tolerate 100 units. 4 developed symptoms after 100 units, though never on the first day this dose was given. One became unconscious on the third day, another became confused, with auditory hallucinations, on the tenth day; the third had a visual hallucination of a large, red, stationary sphere with a green halo, which persisted for ten minutes, and the fourth only became mildly drowsy. The rarity of symptoms is remarkable when one considers Fig. 9 which shows the fluctuations in blood sugar levels during the course of the day in 5 of these patients. This is comparable with

the treatment of schizophrenia, where coma has been known to follow as little as 15 units of insulin yet has failed to appear even after 1,000 units, though the important difference is that schizophrenic patients are starved until coma ensues. In the deliberate production of insulin coma there is also a remarkable variation in blood sugar concentration, patients sometimes being conscious at a level of 25 mg.%, or in coma at 60 mg.%, though they are usually in a state causing alarm if the figure has fallen to 15 mg.%. But twenty years ago it was observed by Sakel (1938) himself that the clinical condition bore little relationship to the simultaneous blood sugar level.

In the past twelve years I have made a diagnosis of clinical hypoglycæmia in 36 patients, rightly or wrongly, and their distribution in the three main ætiological groups is shown in Table I.

TABLE I.—CLINICAL HYPOGLYCÆMIA

| Ætiology | Male | Female | Total |
|---|---|---|---|
| Hyperinsulinism .. .. | 6 | 5 | 11 |
| Post-operative .. .. | 11 | 4 | 15 |
| Psychosomatic .. .. | 4 | 3 | 7 |
| Miscellaneous .. .. | 1 | 2 | 3 |
| Total | 22 | 14 | 36 |

## NEUROLOGICAL MANIFESTATIONS

Although the normal range of blood sugar is somewhat nebulous, major departures from "normal" in either direction may have profound effects on the central nervous system. The *central* nervous system is emphasized because there are no proved direct effects of hypoglycæmia on the cranial or peripheral nerves. Both hypoglycæmia and diabetes may involve the spinal cord, though there are vivid differences between the effects of these conditions on the brain and on the cord. Diabetes may cause coma, which is determined by aceto-acetic acid rather than glucose, but there are no proved examples of chronic diabetic encephalopathy comparable, for example, with diabetic retinopathy. Hypoglycæmia may also cause coma, which may be irreversible or may be followed by permanent brain damage, but there are no progressive forms of hypoglycæmic encephalopathy, excluding the additive effects of recurrent damaging episodes. Conversely diabetes and hypoglycæmia may both produce slowly progressive and not dissimilar forms of amyotrophy, whether this be of central or peripheral origin, but neither condition produces an *acute* cord syndrome (Williams, 1955; Garland, 1957*b*). These differences may be determined phylogenetically.

The glucose demands of the brain vary from one person to another, and from time to time in the same individual. Although the glucose requirements of different parts of the cerebrum vary, so that hypoglycæmia may affect one part of the brain more than another, we might expect hypoglycæmic syndromes to be at least bilateral if not strictly symmetrical, but for some unexplained reason this is not so.

Some of the early and well-known symptoms of over-dosage with insulin, particularly vague sensations of weakness and anxiety, sweating, palpitation, pallor and nausea, are probably determined by the release of adrenaline. These have all been observed frequently in endogenous hypoglycæmia and, apart from disturbances of consciousness, are the most common symptoms in all ætiological groups. They are of great importance and may give the first clue to the diagnosis.

In all the patients in whom I have made a diagnosis of endogenous hypoglycæmia there has been some disturbance of consciousness, apart from 2 with purely amyotrophic syndromes. "Disturbance of consciousness" covers as wide a nosological range as in any other context; it is impossible to list these "dysconscious" states in terms of quantitative or qualitative change, and only some of the more striking aspects will be mentioned. One of the simplest phenomena is for the patient to pass through a phase, lasting for seconds, minutes or hours, during which his behaviour appears to be normal or only slightly disturbed, but for which he later has total amnesia. This resembles the hysterical fugue, though there are two important differences. In the fugue the patient's behaviour will be obviously pathological in retrospect, and the amnesia can always be recovered by various diagnostic tricks; in the hypoglycæmic state behaviour may be apparently normal, though perhaps inappropriate, but the amnesia is permanent and comparable with the post-traumatic state of head injury. In patients with organic hyperinsulinism, but not in the other groups, difficulty in waking in the morning may be an early symptom even though there are no other immediate sequelæ. In all types of endogenous hypoglycæmia attacks of bizarre behaviour, usually with amnesia, are frequent; in these the patient may be confused, often noisy, dysarthric, ataxic, apparently drunk, and even violent. No matter

what the basic cause, most of the patients recorded have had their symptoms for years and they have usually been under treatment for "neurosis" or "psychomotor epilepsy". Complete loss of consciousness may take various forms. The onset of coma may be sudden or gradual, and it may be transient, protracted, or irreversible. In some patients coma is associated with major epilepsy which is indistinguishable from that produced by any of the other multitudinous causes of this symptom. In others phases of coma may not be punctuated by convulsions. Here a parallel may be drawn with the effects of insulin therapy which is occasionally associated with convulsions in the early stages and sometimes when the deepest coma has been produced. Although epilepsy in many forms frequently occurs in the hypoglycæmic state without preceding stupor or coma, it is a curious fact that *status epilepticus* virtually never arises.

The development of irreversible coma has always been a known danger of insulin therapy, and for this reason it is usual to allow deep coma to last for only a few minutes. Irreversible coma resulting from endogenous hypoglycæmia is also of the greatest importance, and many people have died from an insulin-producing tumour when the diagnosis has not been established sufficiently early, for three reasons: Blood sugar estimations may never have been made because the coma was thought to result from some form of intracranial disease; low blood sugar levels have often been observed but ignored; and, in hypoglycæmic coma, blood sugar concentrations may be normal or even in the hyperglycæmic range (Richardson and Russell, 1952). We do not know how long a patient can remain in coma before this state becomes irreversible, but personal experience suggests that after as long as a week there may be "spontaneous" resolution. On the other hand I have seen coma, which was found to be hypoglycæmic within thirty-six hours and appropriately treated, terminate fatally a month later.

An important lesson to be learned from this experience is that unexplained coma should always be treated with intravenous glucose and especially when the previous history is not available; since diabetic coma will have been eliminated I doubt whether this therapeutic test could ever be contra-indicated.

Histological studies show "anoxic" changes, particularly in the cerebral cortex, the basal ganglia, and the cerebellum, and the results of transient disorders arising at these anatomical or physiological levels are clearly seen in non-fatal examples.

Temporary or recurrent dysphasia, hemiparesis and homonymous hemianopia have frequently been observed as hypoglycæmic phenomena, and in one of my patients there was a hemiplegia associated with simultaneous contralateral choreo-athetosis. Occasionally paralyses or dementing states have become permanent, but irreversible neurological syndromes are never progressive and only result from a transitory phase of hypoglycæmic cerebral anoxia which produces neuronal damage.

Disturbances of vision are frequent. Diplopia, with or without squint, is often a premonitory symptom of a hypoglycæmic confusional state, and is a not unusual complaint during the early stages of insulin therapy in those patients capable of remembering their experiences. Macropsia, micropsia, chromatopsia and more complex visual hallucinations, sometimes resembling those of mescaline intoxication, have also been observed; the pathophysiological basis is unknown though such disorders probably arise from temporal lobe dysfunction. Olfactory hallucinations and parosmia may arise.

Rotatory vertigo of hypoglycæmic origin has been an important discovery, especially as this may be the only clinical manifestation of endogenous hypoglycæmia (Moorhouse, 1956). In my experience the patients usually complain of the sudden onset of dizziness with a rotatory element, either subjective or objective, sometimes coming on so precipitately that they fall to the ground, and often associated with nausea and vomiting. The duration of the vertigo usually varies from a few minutes to about an hour, though occasionally it has been more prolonged. I have not had the opportunity of examining any of these patients during an attack, but in none was there concomitant deafness or tinnitus, suggesting that function is disturbed at a non-labyrinthine level. Vertigo frequently arises during insulin therapy, and many patients are observed to be ataxic several hours after coma has been terminated. Analogy with visual and auditory hallucinations, as well as with observations during cortical stimulation in the conscious patient (Penfield and Rasmussen, 1950), makes it probable that rotatory vertigo also results from a disturbance of function in the temporal lobes. Further weight is lent to this view by the finding of maximal or asymmetrical EEG changes in the temporal region during hypoglycæmia (Garland, 1957), and by histological confirmation of "anoxic" damage which may be most severe in the temporal cortex, including Ammon's horn. I am not familiar with permanent or even temporary blindness, deafness, loss of the senses of smell or taste, or of phasic depression resulting from hypoglycæmia. Narcolepsy and cataplexy, however, may be associated with low blood sugar levels, and then the clinical syndrome and the biochemical deviations are

probably both the result of hypothalamic dysfunction; even so, dietetic restriction may be of therapeutic value in a syndrome which is often very resistant to medicinal treatment.

All the transient disturbances resulting from hypoglycæmia tend to be accompanied by excessive sweating and are sometimes followed by excessive hunger; headache and vomiting are not infrequently associated.

Many people must have died in hypoglycæmic coma resulting from organic hyperinsulinism, but I am not aware of death from post-operative hypoglycæmia though I suspect that this variety may cause prolonged, and possibly irreversible, coma; psychosomatic hypoglycæmia appears to be the least sinister form, and is only potentially fatal.

Hypoglycæmia may determine a clinical picture simulating that of motor neuron disease, but this is not likely to be recognized unless the picture of widespread muscular weakness and wasting, with fasciculation or other accompaniments, is interspersed by episodes of disturbed consciousness (Williams, 1955). The diagnosis of motor neuron disease should perhaps never be made until adequate tests for organic hyperinsulinism have proved to be negative. It may well be that, if not treated, hypoglycæmic amyotrophy can be fatal. I have not been able to establish this diagnosis myself though I have at present under observation two suspected patients (Fig. 10). The scanty references to proved examples of

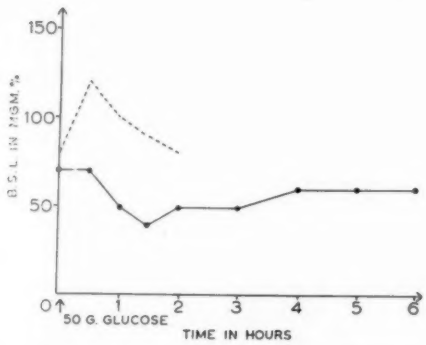



FIG. 10.—Probable hypoglycæmic amyotrophy.

hypoglycæmic amyotrophy make it fairly certain that this syndrome is frequently overlooked, usually being dismissed as motor neuron disease. As far as is known hypoglycæmic amyotrophy is only produced by organic hyperinsulinism; appropriate surgical treatment can certainly arrest the process or even reverse it.

## CONCLUSIONS

Innumerable observations have been made on all forms of hypoglycæmia by neurologists, psychiatrists, biochemists, and even general physicians, and many conclusions are incontrovertible. In spite of this, however, my feeling is that we are still only on the fringe of knowledge, especially regarding endogenous hypoglycæmia. Many examples are overlooked because the diagnosis is never considered. Abdominal operations are carried out needlessly on inadequate criteria, or are failures through lack of diagnostic panache. Scientific proof often escapes us, but clinical impression and the undoubted value of appropriate dietetic therapy can still reduce the considerable morbidity and, it may be, mortality. In this condition, as in many others, laboratory aids, though frequently invaluable, may prove to be both a clinical snare and an academic delusion.

*Acknowledgments.*—I should like to thank Professor G. H. Lathe for his valuable advice; several surgical colleagues for allowing me to carry out pre- and post-operative glucose tolerance tests; Dr. F. W. Sutherland for the histological studies; my ex-house physicians Dr. Pamela Barker and Dr. Lois Gendall for producing the illustrations; and, especially, Dr. Doreen Moorhouse who has allowed me to draw freely on her thesis for the M.D.(Leeds) and given other advice and criticism.

## REFERENCES


BIRKINSHAW, V. J., GURD, M. R., RANDALL, S. S., CURRY, A. S., PRICE, D. E., and WRIGHT, P. H. (1958) *Brit. med. J.*, ii, 463.

BRAZIER, M. A. B., FINESINGER, J. E., and SCHWAB, R. S. (1944) *J. clin. Invest.*, **23,** 313, 319.

BREIDAHL, H. D., PRIESTLEY, J. T., and RYNEARSON, E. H. (1956) *J. Amer. med. Ass.*, **160,** 198.

COHEN, H. (1950) *Ann. R. Coll. Surg. Engl.*, **6,** 3.

CONN, J. W. (1940*a*) *Amer. J. med. Sci.*, **199,** 555.

—— (1940*b*) *J. Amer. med. Ass.*, **115,** 1669.

——, and SELTZER, H. S. (1955) *Amer. J. Med.*, **19,** 460.

FARQUHAR, J. W. (1956) *Arch. Dis. Childh.*, **31,** 203.

FRASER, R., MACLAY, W. S., and MANN, S. A. (1939) *Quart. J. Med.*, **7,** 115.

GARLAND, H. (1957*a*) *Brit. med. J.*, ii, 969.

—— (1957*b*) In: Modern Trends in Neurology. Editor: D. Williams. London; p. 229.

GOMORI, G. (1939) *Amer. J. Path.*, **15,** 497.

HOWLAND, G., CAMPBELL, W. R., MALTBY, E. J., and ROBINSON, W. L. (1929) *J. Amer. med. Ass.*, **93,** 674.

LAIDLAW, J., and RAB, S. M. (1957) *J. Neurol. Psychiat.*, **20,** 260.

MARTIN, D. B., RENOLD, A. E., and DAGENAIS, Y. M. (1958) *Lancet*, i, 76.

MEDWID, A., WEISSMAN, J., RANDALL, H. T., BANE, H. B., VANAMEE, P., and ROBERTS, K. E. (1956) *Ann. Surg.*, **144,** 953.

MOORHOUSE, D. (1956) *Brit. med. J.*, ii, 1512.

MUIR, A. (1949) *Brit. J. Surg.*, **37,** 165.

NERENBERG, S. T. (1954) *Amer. J. clin. Path.*, **24,** 27.

NICHOLLS, A. G. (1902) *J. med. Res.*, **8,** 385.

PENFIELD, W., and RASMUSSEN, T. (1950) The Cerebral Cortex of Man. New York.

RICHARDSON, J. C., and HILL, F. M. (1957) *Neurology*, **7,** 793.

RICHARDSON, J. E., and RUSSELL, D. S. (1952) *Lancet*, ii, 1054.

SAKEL, M. (1938) *Amer. J. Psychiat.*, **94** (suppl.), 24.

SUTHERLAND, E. W., and DE DUVE, C. (1948) *J. biol. Chem.*, **175,** 663.

THOMPSON, R. H. S., and KING, E. J. (1957) Biochemical Disorders in Human Disease. London.

VALLANCE-OWEN, J., and HURLOCK, B. (1954) *Lancet*, i, 68.

WHIPPLE, A. O. (1938) *J. int. Chir.*, **3,** 237.

WILDER, R. M., ALLAN, F. N., POWER, M. H., and ROBERTSON, H. E. (1927) *J. Amer. med. Ass.*, **89,** 348.

WILLIAMS, C. J. (1955) *Brit. med. J.*, i, 707.

WYKE, B. D. (1952) *Electroenceph. clin. Neurophysiol.*, **4,** 339.

# Section of Laryngology

President—R. J. Cann, M.S., F.R.C.S.

[*May* 2, 1958]

## A Possible Relationship Between the Sinuses and the Lymphoid Tissue of the Nasopharynx

By A. J. Moffett, T.D., F.R.C.S.

*Birmingham*

No part of the body is an island entire of itself. It may be given its anatomical beginnings and endings, but physiologically it is associated with every other part of the body, and what happens in one part will affect to a greater or lesser degree what happens in any other. This interdependence is particularly marked in the relationship between the nasal sinuses and the lymphoid tissue of Waldeyer's ring.

Enlargement of the lymphoid tissue in this area is often associated with infection in the nose or nasal sinuses.

A very marked enlargement of the tonsils and other lymphatic collections may occur without any appreciable interference with the health of the individual. This should probably be regarded as a functional, as opposed to a pathological, enlargement and is the not unusual response of an organ to increased demand upon its services. Such an enlargement cannot be regarded as being of any particular significance and is usually symptomless. It may well be of benefit to the patient unless the hypertrophy is so marked that mechanical obstruction to swallowing or respiration occurs. If, however, the progress continues, mechanical obstruction does occur, and the onset of infection converts a functional enlargement into a pathological hypertrophy. It is a common observation to find that one tonsil is considerably larger than the other and this enlargement is due to demands made upon its activities by an infection in the nose or nasal sinuses on that side.

Probably even more significant is the marked enlargement, after removal of tonsils and adenoids, of the remaining elements of Waldeyer's ring if an infection, present in the nose or sinuses, has not subsided or been cleared up by treatment. This enlargement of what were quite insignificant particles of lymphoid tissue, in an attempt to shoulder the responsibilities of that already removed, is a cause of many so-called tonsil remnants in children. In adults it usually appears as a band of fleshy lymphatic tissue behind the posterior pillars of the fauces, or as a marked enlargement of the lymphoid tissue in the base of the tongue.

These everyday clinical observations suggest that there is a very close relationship between the sinuses and the pharyngeal lymphatic tissue and that much of the lymphatic drainage from the sinuses is by surface mechanism rather than by lymphatic vessels.

An attempt will be made in this paper to show how these things may occur and to indicate some of the functions which these organs may perform. The work referred to in this paper has been done on the more accessible members of these two systems: the antrum of Highmore and the pharyngeal tonsil, and it is to these that reference will generally be made.

Several functions of the nasal sinuses have been listed by StClair Thomson and Negus (Thomson, 1955). Lightening the bones of the skull, acting as resonators, acting as insulators, or merely being areas over which the olfactory mucosa once spread, are the most likely. The production of secretion is the only one which is quite certain.

So far as the tonsils are concerned the list of possible functions is even longer; Logan Turner (1921), however, reduces the number to 4, which are:

(1) Production of lymphocytes.
(2) Phagocytosis by young polymorphs.
(3) Elimination in acute infection, the inflammation being secondary and not primary.
(4) Antibody formation, immunization and vaccination of the body.

With the last of these functions I am particularly concerned and I shall endeavour to indicate how the tonsils in association with the nasal sinuses may be concerned in the establishment and maintenance of immunity to airborne infection. I shall mention briefly the normal activities which occur in the nasal sinuses, and also indicate some of the characteristics of the lymphoid tissue of Waldeyer's ring as typified by the pharyngeal tonsil.

*Sinuses*

(1) In the antrum, regarding it as a typical sinus, if the ostium is patent, there is during inspiration and expiration a very marked variation in the air pressure in that sinus. A strong sniff will produce a negative pressure of as much as 800 mm. water, an expiratory snort about two-thirds of that pressure (O'Malley, 1933, 1935). This means that the air within the sinus is kept continually moving and as a result small samples of air continue to be offered to the sinus. Each sample of air taken in carries with it some of the organisms or particles which have escaped the protective mechanism of the nasal mucous membrane.

(2) In order that those foreign bodies which enter the sinus may not collect in that respiratory backwater like corks in slack water, an elaborate cleansing mechanism exists. This basically consists of a layer of mucus lining the whole of the sinus and kept in motion by ciliary action. The rate of flow is half to one centimetre per minute. The direction of the flow of this mucus is such that it is carried round and round the antrum in a spiral until it is twisted into a thread and evacuated through the ostium (Hilding, 1932). This spiral action accounts for the tadpole-like appearance often seen in blobs of mucus which have been removed during an antrum wash-out.

(3) The fact that the sinuses are continually being ventilated by air carrying organisms, but on the whole remain remarkably free from infection, suggests that the mucus of a sinus contains some inhibiting substance, similar in character to the lysozyme found in tears (Fleming, 1929). The mucus can be reinforced if necessary by leucocytes or other free cellular elements derived from the lining membrane.

(4) The mucus, having been evacuated by the cleansing mechanism of the sinus, enters the nasal cavity and follows well-defined paths leading backwards into the nasopharynx and at some point in its progress flows over the lymphatic tissue of Waldeyer's ring.

Certain factors interfere with the proper cleansing of a sinus. Local conditions include anatomical malformations, atrophy, congestion from infection or allergy, and the use of certain drugs (Proetz, 1934).

General factors are of even greater importance. It can be shown experimentally that the ciliary activity of the sinus mucosa is slowed or weakened in an exhausted or debilitated subject and the character of the mucus may be changed so that it is too tenacious or too fluid to function properly (Lucas, 1932). The corollary to this is, of course, that an infection of the sinus may not be a disease in itself, but merely a reaction to the general state of health of a particular individual. A sinus infection may be, in fact, not a disease but a symptom.

*Waldeyer's Ring and the Tonsils*

Waldeyer's ring is a collection of lymphoid tissue surrounding the pharynx, and the pharyngeal tonsil is usually the largest conglomeration of lymphoid tissue in it. Basically the tonsil is a test tube or rather a series of test tubes made of polyhedral epithelium, forming crypts and surrounded by a collection of lymphoid tissue. It is not, however, ordinary lymphoid tissue such as may be found in a cervical gland. It is a specific type known as epithelial lymphatic tissue and has the following characteristics:

(1) It has one surface covered with the epithelium of the tube or organ in which it is situated.

(2) It has efferent but no afferent lymphatic vessels. Lymphatic vessels drain from it, but none drains into it.

(3) It develops only in areas which are likely to be exposed to surface sepsis; the tonsils, Peyer's patches, and the vermiform appendix being principal examples.

(4) Its development becomes much more marked when the region in which it is situated becomes exposed to infection. Thus the enormous appendix of the rabbit shows little development until the baby rabbit has stopped suckling and started to eat grass, and the tonsil of the child becomes enlarged during the first term at school.

(5) It is reputed to be immune to the lymphadenopathies such as Hodgkin's disease which may affect other glands (Clark, 1939).

(6) In addition to these characteristics the pharyngeal tonsil is so cradled between the anterior and posterior pillars of the fauces that when the act of swallowing takes place the tonsil is squeezed into its bed. This is the reverse action to retching which presses the tonsil out of the bed and towards the mid-line.

Anybody who has guillotined a tonsil will not doubt this powerful contracting force. It is possible to dissect a tonsil in an unrelaxed swallowing patient, in spite of the anæsthetist, but it is not possible to guillotine one.

*The Movement of Mucus in the Nasopharynx*

To a lesser extent some form of pressure is exerted during swallowing on practically all the lymphatic tissue in Waldeyer's ring.

By the use of an indicator it is possible to discover the fate of some of the particles removed from the sinus by ciliary action.

In this investigation Indian ink was used as the indicator and work was done on the antrum only. Using a quantity of indicator as small as 0·5 ml., it was found that there was a great variation in time taken for the indicator to appear and also in the time it remained in the antrum. In some cases it was visible almost immediately and in others not for several hours. In one case there was no drainage for twenty-four hours and the ink continued to appear for four days. Twelve days after the injection the antrum was washed out and a large quantity of ink still remained inextricably mixed with mucopus.

It is possible that if a powder could be insufflated into an undisturbed antrum the time taken to appear would be considerably longer. It is obvious that the swilling out of the antrum with saline must disturb the mucus usually found there and probably produce an unusual degree of activity.

*Phagocytosis Within the Antrum*

In 22 cases in which Indian ink was injected into the antrum, the antrum was subsequently washed out and the washings examined for traces of carbon particles. In 12 cases the wash-out was clear. In the remaining 10 cases some of the ink was found, and all these were subjected to microscopic examination. In 8 cases the carbon was merely mingled with the mucus, and if pus cells were present it was entirely extracellular. In 2 cases it was found that an active phagocytosis of the carbon particles had occurred and that much of the black material present was contained in cells so laden with pigment, shown in Fig. 1, that it was difficult or impossible to identify the type.

This active phagocytosis by free cellular elements does not appear to depend on the quantity of ink in the antrum, nor on the length of time it has lain there. It appears from this that the stimulus to phagocytosis is not produced solely by the local reaction to the carbon particles. There is need for some factor affecting, presumably, the patient's general condition, to produce the necessary response.

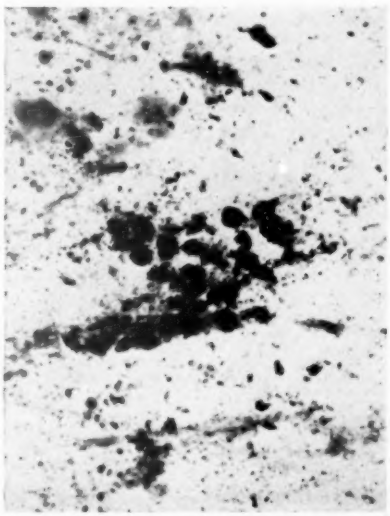


FIG. 1.—Phagocytosis by pus cells in antrum mucus. (× 420.)

According to Lowndes Yates (1924) the trickles of mucus from the various sinuses were tributaries of one common stream which formed just below the eustachian tube. From there the stream flowed downwards, with an invariable side stream into the tonsil bed. He used 10 ml. of 0·4% solution of indocarmine and found that the dye usually appeared in two minutes. It would be unusual for such a large quantity of fluid to be found in an antrum. Compared with the centimetre per minute snail-pace ciliary action, 10 ml. of 0·4% solution of indocarmine must be a raging torrent. The streams charted could well be the overflow of a blue river in spate rather than the course taken by the normal secretion of mucus.

If the stream of mucus which flows down to the nasopharynx is sufficiently slow it invariably enters the tonsil bed and flows over part of the tonsil. Assuming that the flow is coming from one side only, as soon as the subject swallows the particles of pigment are smeared over the tonsil, the lingual tonsil, the lymphatic patches on the posterior pharyngeal wall, and very often on to the tonsil on the other side. The excess is generally swallowed, but some may enter the larynx. The effect of the act of swallowing is to squeeze the ink on the surface of the tonsil deeper into the crypts and in such quantities that it can in many cases be seen there with the naked eye, and displayed hours or days later, under the microscope.

At this point of investigation there was no doubt that the particles of ink removed from an antrum by the stream of mucus are carried into the nasopharynx and some at least enter the tonsillar crypts. The presumption was that they would be taken up by the cellular elements of the tonsil or absorbed into it in some way.

Supplying a tonsil with Indian ink by re-filling the antrum every day for several days was not considered practicable. Therefore, one drop of ink was painted on the tonsil a few hours or days before tonsillectomy, and the tonsil examined and sectioned on removal. Numerous attempts to trace the ink coming from the antrum or applied to the surface of the tonsil any further than the crypts were met by failure.

Some 36 cases were examined without conclusive evidence of absorption of carbon particles into the tonsil. At times small specks of material suggestive of the carbon were seen apparently in the surface cells of the tonsil or in the subjacent cells. A carbon particle is a particularly difficult object to identify under the microscope. It appears brownish and is definitely refractile under high magnification. It was not possible to say with certainty that the absorption of particulate bodies by the cells had taken place. However, as phagocytosis in the antrum of carbon particles was known to occur only occasionally and under certain specific conditions which were unknown, the experiments were not abandoned, in the hope that one day the necessary specific conditions would in fact arise.

In the 37th tonsil these special conditions, whatever they may be, did arise, and it was possible to demonstrate, not once, but on other occasions, particles of carbon, not only in the crypts, but in the substance of the tonsils and in the actual cells (Fig. 2).

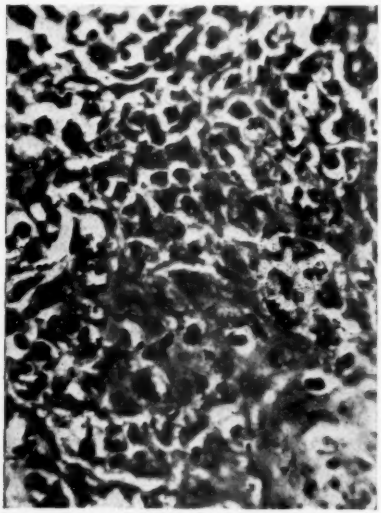


FIG. 2.—Cells laden with carbon in the tonsil tissue. (× 420.)

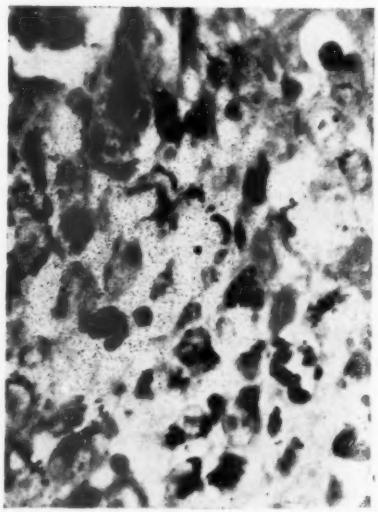


FIG. 3.—Carbon-laden cells in tonsil tissue. (× 675.)

If a cell accepts carbon particles it accepts them in such a whole-hearted manner that the identity of the cell is almost completely blacked out.

If only one or two particles are seen, doubt may be held about their authenticity. Occasionally, however, cells are only partially filled with pigment and some attempt at identifying them may be made. Several cells are shown in Fig. 3, some being possibly mast cells and others reticulo-endothelial cells.

In no section has there been any evidence that these particles enter the germ centres, which of course are the conglomeration of cells associated with the formation of new lymphocytes.

When pigment penetrates the tonsil it appears to do so at the bottom of the crypts where the cells lining the crypts become less differentiated than those of the surface of the tonsil. Having entered the tonsil the appearance of some of the sections suggests that the particles travel through the lymphatic sinuses and farther than that they have so far not been traced. It seems probable that the particles would eventually pass right through the tonsil and enter the efferent vessels.

*Conclusions*

(1) The normal lymphatic drainage of the sinuses is by means of a surface mechanism which enables the cleansings of the sinuses to be carried to the epithelial lymphatic system of Waldeyer's ring. It is probable that drainage into the deep lymphatics of the head and neck occurs only when the protective pellicle of mucus has been penetrated. It is possible that the crypts in the tonsils play the part of the afferent vessels of the lymphatic glands.

(2) Organisms presented to the epithelial-lymphatic system are either dead or in an inhibited state which enables them to be dealt with by the lymphatic tissue, without active infection arising. This would produce the ideal arrangement for absorption of organisms or their products into the body for the production of immunity.

REFERENCES

CLARK, W. LE G. (1939) Tissues of the Human Body. Oxford.
FLEMING, A. (1929) *Lancet*, i, 217.
HILDING, A. (1932) *Amer. J. Physiol.*, **100**, 664.
LUCAS, A. M. (1932) *Amer. J. Anat.*, **50**, 141.
O'MALLEY, J. F. (1933) *J. Laryng.*, **48**, 309.
—— (1935) *J. Laryng.*, **50**, 389.
PROETZ, A. W. (1934) *J. Laryng.*, **49**, 557.
THOMSON, StC. (1955) Diseases of the Nose and Throat. 6th ed. Revised by V. E. Negus. London.
TURNER, A. L. (1921) *J. Laryng.*, **36**, 79.
YATES, A. L. (1924) *J. Laryng.*, **39**, 554.

# Section of Laryngology with Section of Otology

JOINT SUMMER MEETING HELD AT THE ROYAL COLLEGE OF SURGEONS OF EDINBURGH

## OTOLOGICAL SESSION

Chairman—I. SIMSON HALL, F.R.C.P.Ed., F.R.C.S.Ed.
(President of the Section of Otology)

[*June* 27, 1958]

A DISCUSSION on **Acoustic Neuroma** was opened by DR. M. R. DIX, DR. C. S. HALLPIKE, and PROFESSOR NORMAN M. DOTT.

PROFESSOR NORMAN M. DOTT read a paper on **Facial Paralysis—Restitution by Extrapetrous Nerve Graft.**

*See* November *Proceedings*, p. 889.

## LARYNGOLOGICAL SESSION

Chairman—R. J. CANN, M.S., F.R.C.S.
(President of the Section of Laryngology)

[*June* 28, 1958]

A DISCUSSION on **The Dysphonias and the Scope of Speech Therapy in their Treatment** was opened by Mr. MAXWELL P. ELLIS and Mr. LEONARD WILLMORE.

Subsequent speakers were Mr. R. L. FLETT, Mr. I. G. ROBIN, Mr. R. G. MACBETH, Mr. D. ANGELL JAMES and Mrs. FLORENCE CAVANAGH.

Dr. MILES TAYLOR read a paper on **The Histochemical Characteristics of the Normal and Abnormal Nasal Respiratory Mucosa.** It was discussed by Mr. MAXWELL P. ELLIS and Mr. LIONEL TAYLOR.

The meeting will be reported in the *Journal of Laryngology*.

## BOOKS RECEIVED FOR REVIEW

**Adams (J. C.).** Outline of fractures including joint injuries. 2nd ed. pp. viii + 268. Edinburgh and London: Livingstone. 27s. 6d. 1958.

**Beaudette (F. R.),** ed. Progress in psittacosis research and control. pp. xii + 271. New Brunswick, N.J.: Rutgers University Press. $5 1958.

**Blackburn (G.),** and **Lawrie (R.),** eds. Textbook of surgery. pp. xii + 1122. Oxford: Blackwell. 84s. 1958.

**Casson (F. R. C.).** It's healthy to be human. pp. 160. London: British Medical Association. 10s. 6d. 1958.

**Clarke (A. M.),** and **Clarke (A. D. B.),** eds. Mental deficiency. The changing outlook. pp. xvi + 513. London: Methuen. 45s. 1958.

**Gardiner-Hill (H.).** Clinical involvements or—The old firm. pp. vii + 200. London: Butterworth. 32s. 6d. 1958.

**Hargreaves (G. R.).** Psychiatry and the public health. pp. 118. London: Oxford University Press. 12s. 6d. 1958.

**Hetherington (W.).** The compend. Addendum for the year 1957. pp. 74. Bristol: Wright. 5s. 1958.

**Hutton (I.).** Woman's change of life. pp. 124. London: Heinemann. 6s. 1958.

**Jordan (H. H.).** Hemophilic arthropathies. pp. xv + 255. Springfield, Ill.: Thomas. Oxford: Blackwell. 63s. 1958.

**Monrad-Krohn (G. H.).** Clinical examination of the nervous system. 11th ed. pp. xx + 466. London: Lewis. 40s. 1958.

**Montgomery (G. L.).** Pathology for students of dentistry. 2nd ed. pp. vii + 307. Edinburgh and London: Livingstone. 40s. 1958.

**Negus (Sir Victor).** Comparative anatomy and physiology of the nose and paranasal sinuses. pp. xv + 402. Edinburgh and London: Livingstone. 70s. 1958.

**Roberts (H. J.).** Difficult diagnosis. A guide to the interpretation of obscure illness. pp. xi + 913. Philadelphia and London: Saunders. £6 13s. 1958.

**Ulrich (R.).** Coffee and caffeine. Trans. J. Ellingham. pp. 52. Bristol: Wright. 7s. 6d. 1958.

**Walshe (Sir Francis).** Diseases of the nervous system. 9th ed. pp. xvi + 373. Edinburgh and London: Livingstone. 30s. 1958.

**Wynn-Parry (C. B.).** Rehabilitation of the hand. pp. vii + 273 + 17. London: Butterworth. 45s. 1958.

JOINT MEETING No. 2

# Section of Experimental Medicine and Therapeutics with Section of Neurology

Chairman—J. V. DACIE, M.D., F.R.C.P.

(President of the Section of Experimental Medicine and Therapeutics)

[*May* 13, 1958]

## DISCUSSION ON TETANUS

**Professor G. Payling Wright** (London):

*The Use of A.T.S. in the Treatment and Prophylaxis of Tetanus*

After the discovery of tetanus antitoxin in 1890 by von Behring and Kitasato, nearly a decade elapsed before the specific serum came into general use as a prophylactic agent. It seems likely that this delay may be largely attributed to disappointment with antitoxin in the treatment of established tetanus, and its very unfavourable comparison in this respect with the much more successful diphtheria antitoxin which was introduced into medicine almost at the same time. However, the widespread realization that, even if of limited value in treatment, it was capable of contributing usefully in prophylaxis, followed the publication by Nocard (1897) of the notable success obtained through its use in eliminating tetanus as a complication of animal surgery.

So far as I am aware, no observations comparable with those of Nocard have ever been made on human beings. With so serious a disease, ethical considerations preclude a properly controlled therapeutic trial on man. But the records of the incidence of tetanus amongst the wounded during the early months of the First World War are so striking that no inference other than that the serum possesses protective power can explain the dramatic fall in the morbidity and mortality of the disease that followed the general issue of tetanus antitoxin in October 1914 (*see* Bruce, 1920). In spite of the very encouraging success disclosed by these wartime statistical studies, there has remained a residuum of failures—the cases termed by the French "tétanos post-sérique"—it is these that might be further reduced in number were we to appreciate better some of the limitations inseparable from all passive immunological procedures that employ injections with sera from an alien species.

Two important new technical methods introduced into immunology have added greatly to our knowledge of the fate of foreign proteins, such as the specific antitoxic globulin of horse serum—their distribution in the tissues and their metabolic destruction by intracellular digestion—after injection into the body. The first of these methods depends upon the use of specific antibodies to the foreign protein which, without loss of their specificity, have been coupled to the dye fluorescein, so that examination of the tissues under ultraviolet light discloses the site of deposition of the foreign protein through the brilliant fluorescence of local accumulations of the antigen-antibody complex. The second method depends upon the labelling of the foreign protein with some radioactive isotope, such as iodine or sulphur, so permitting both the destination of the injected material to be determined and its subsequent metabolic degradation to be followed quantitatively by examinations of the blood and urine. As a result we have now acquired a passably clear idea of the fate of many foreign proteins—their localization in part in the connective tissues, notably those of the skin and joints, and their ingestion in part by the antibody-forming cells of the reticulo-endothelial system in whose cytoplasm they eventually undergo digestion.

Since the specific antitoxic agent in antitetanus serum is usually one of the gamma globulins of the horse, it should not be a matter for surprise that it, like all other heterologous proteins, is steadily destroyed in the tissues and rendered correspondingly ineffective as a protective agent. What is of practical importance in the prophylaxis of tetanus is the

length of time taken for this destruction to be brought about, and how that compares with the time required by the clostridium to elaborate dangerous quantities of its toxin in the infected structures. Some indication of this latter time is provided for man by the incubation period of the disease—commonly some ten to fourteen days—as well as by animal experiments in which the rate of toxin production at a site of infection can be estimated by serial immunological titrations. Such animal assays have disclosed what seems seldom fully appreciated, that when they become moribund such infected animals may have a thousand or more lethal doses of toxin in the tissues surrounding the wound, and that in man, who ranks amongst the more highly susceptible of the mammals to tetanus, the same great excess of toxin may be present. The rate of loss of the prophylactic antitoxin, on the other hand, can be determined with some accuracy by the use of appropriate immunological techniques. I shall now mention the results of two such studies on the duration of immunity: in the first, 100,000 units of antitoxin were given, in the second, the more usual prophylactic dose of 1,500 units was employed.

Cooke and Jones (1943) have followed the progressive fall in the concentration of tetanus antitoxin in the serum of six small children after the injection of 100,000 units; their findings are set out in simplified form in Table I. By the end of four weeks, the concentration

TABLE I.—AVERAGE ANTITOXIN TITRES IN THE SERUM OF SIX CHILDREN AFTER INOCULATION WITH 100,000 UNITS OF A.T.S. (COOKE AND JONES, 1943)

| Days after injection | Antitoxin units/ml. |
|---|---|
| 3–4 | 27 |
| 9 | 15 |
| 14 | 5 |
| 21 | 2 |
| 28 | 1 |
| 35 | 0·4 |
| 42 | 0·2 |
| 49 | 0·1 |

had fallen to one unit per millilitre of serum, and three weeks later it had further declined to one-tenth of that figure. The results in Bigler and Werner's (1941) series, in which 1,500 units were given to children, are summarized in Table II. As might be anticipated from

TABLE II.—AVERAGE ANTITOXIN TITRES IN THE SERUM OF 64 CHILDREN AFTER INOCULATION WITH 1,500 UNITS OF A.T.S. (BIGLER AND WERNER, 1941)

| Week | Units |
|---|---|
| Second | 0·2 |
| Third | 0·01 |
| Fourth | <0·003 |

the smaller dosage used, the maximum titre obtained was very much lower and the period of persistence of estimable amounts of antitoxin much shorter. By the end of the third week, it had fallen on average below the value of one-hundredth of a unit in each millilitre of serum.

I shall now consider briefly the practical implications of these antitoxin decay curves. Here we are under a noteworthy disadvantage when immunity in tetanus is compared with that in the not very dissimilar disease diphtheria. For with diphtheria, the Schick test—with its estimation of whether or not a critical level of antitoxin is present in the tissue fluids—provides a fairly accurate index of immunity or susceptibility. A serum concentration of between one-thirtieth and one-hundredth of a unit of diphtheria antitoxin lies, we infer from numerous investigations, at the borderline of protection. With tetanus no such simple test is available, so that we have no comparable well-defined quantitative guide to aid us. But from a diversity of sources—observations on human beings and experiments on animals—the impression has been gained that with tetanus a protective serum level lies somewhere between one-tenth and one-hundredth of a unit. If now we refer back to Cooke's and to Bigler's studies, we might reasonably infer that the very large dose of antitoxin given by the former probably provides protection on average for about seven weeks, while the smaller amount, commonly used in this country for prophylactic inoculations, in most instances loses its effectiveness towards the end of the third week. But these conclusions are based on statistical considerations, and the variability from person to person is far from inconsiderable. It may well be that some instances of "tétanos post-sérique" are attributable to the unhappy conjunction of a capacity to destroy foreign proteins with unusual rapidity, and of an infection with a strain of the clostridium that elaborates its toxin rather slowly.

Attempts have been made to obviate this eventuality and to prolong the period of protection by one or more repetitions of the injection of the antitoxin. I shall now consider the likely results of this procedure and the important hazard it may involve. I shall omit any reference to immediate or delayed anaphylactic reactions or to those of a neurological character described fully by Miller and Stanton (1954), but will confine myself to the specific bearing of multiplying serum inoculations on the effectiveness of prophylaxis in tetanus.

The antibody-forming elements in the tissues become trained to a prompter and more vigorous execution of their specific activity by repetition of exposure to the antigen. This principle, indeed, underlies our current practice of multiple inoculations with non-living antigens such as toxoids and vaccines. But the phenomenon is typical of the immunological responses to all heterologous antigens, and horse serum proteins in man are no exception.

It would be ungracious if I failed here to recall the pioneer investigations upon the "secondary response" and its implications made by Glenny and his associates—observations which have since led others to the study of this fundamental phenomenon. The more recent introduction of radioactive isotopes as labels for antigenic proteins has enabled the experimentalist to display the more than additive effect of repeated exposure with much greater precision than with the less exact techniques of serology. I shall restrict myself here in the main to recent studies employing isotopic labels, and will review briefly two that exemplify this general principle of "immunological education".

The first is from amongst Professor Wormall's valuable series of investigations on biochemical aspects of immunology. In this publication Francis *et al.* (1957) displayed unequivocally the very differing rates of removal of a foreign protein—a horse gamma-globulin—from the blood of normal and specifically immunized rabbits. By the end of half an hour, some three-quarters of the injected protein was still in the circulation of the former, whereas less than one-tenth remained in the blood of the immunized animals. These rates of removal are notably pertinent to the problem of passive protection against tetanus, firstly because the foreign protein used was that which carries the antitoxic properties of the specific serum, and secondly, because the quantity of protein that they injected, about two milligrams for each kilogram of body weight, is almost the same as that present in the prophylactic dose of the antitoxin preparation now usually employed. It is this correspondence between both the nature and the dosage of his antigen and the prophylactic agent for tetanus that makes Wormall's estimates of the effects of prior immunization so relevant to our present discussion.

The second study was made some years ago by Laws and myself (Laws and Wright, 1952), and our findings agree well with those of Wormall. We used both bovine serum albumin and serum globulin, and again injected these proteins in amounts closely commensurate with that present in specific antitoxic serum. But Laws (1952) carried the investigation rather further, for in order to find out whether this accelerated loss from the circulating blood in immune animals was brought about by the more rapid re-distribution of the proteins between the intra- and extravascular body fluids or by their more prompt removal and destruction by reticulo-endothelial cells, he examined the urines of the two groups of animals for their content of labelled degradation products. In both groups, isotopically-labelled polypeptide fractions were recoverable, but their earlier appearance and greater quantity in the urine of the immunized rabbits shows that "immunological education" goes further than an accelerated abstraction of the foreign protein from the blood—it also involves its more rapid destruction by the cells that remove it.

The progressive loss of immunizing power of antitoxin that results when one inoculation of serum follows another was recognized some twenty years ago by Ramon and his associates, and the finding was not without influence upon him in his campaign for the obligatory active immunization of all children against tetanus. Together with Falchetti of Sienna, Ramon (1935) titrated the antitoxin content of the blood of rabbits after successive inoculations: the first led to the development of a protective level that lasted for about a week, the second to a much lower maximal value and shorter persistence and the third to one that conferred no significant protection at all.

An unusual case of tetanus, recorded by Littlewood, Mant and myself (1954), illustrates very clearly the false sense of security that may be engendered by the administration of antitoxin to an injured person who happens to have had previously an inoculation of either tetanus or diphtheria antitoxin—for both these prophylactics are almost invariably prepared in horses and share the antigenic properties of this foreign species:

> A schoolboy, aged 14, severely injured his hand while experimenting with a home-made bomb. On admission to hospital, he received 1,500 units of tetanus antitoxin and an extensive course of penicillin. After appropriate surgical treatment, including skin grafting, he was discharged. Almost exactly six months later he was readmitted with very similar injuries caused by the explosion of a second almost identical home-made bomb. He again received 1,500 units of tetanus antitoxin and

a course of penicillin, but on the twelfth day he developed trismus and stiffness of the erector spinæ muscles and the diagnosis of tetanus was made. When a test dose of horse serum was inoculated a mild urticarial response developed at the site, but after desensitization was believed to have been accomplished, an intravenous injection of one-tenth of a millilitre of antitoxin was followed by a severe generalized reaction. Eventually, 100,000 units of antitoxin were given intravenously but the signs of tetanus increased in severity and the boy died seventeen days after his injury.

It seems hard to escape the conclusion that the supposedly prophylactic inoculation of antitoxin after the second accident had failed because the inoculation six months before had induced an immunity to horse serum with its consequent accelerated destruction of the specific serum globulins.

The moral to be drawn from this cautionary story is quite clear. As Littlewood, Mant and I urged in discussing the implications of this case: "Once a person has received an injection of any horse serum antitoxin, irrespective of the disease for which it may have been given, that person should be promptly immunized against diphtheria and tetanus with the appropriate toxoid. By thus creating the state of active immunity, which can be effected without any unpleasant side-effects, any future need for passive protection against these diseases with horse serum antitoxin is rendered unnecessary. Furthermore, before any surgical measures are undertaken in tissues which have been previously traumatized and may in consequence harbour contaminating tetanus spores, active immunization should always be carried out beforehand as a precautionary measure."

## REFERENCES


BIGLER, J. A., and WERNER, M. (1941) *J. Amer. med. Ass.*, **116**, 2355.
BRUCE, D. (1920) *J. Hyg. Camb.*, **19**, 1.
COOKE, J. V., and JONES, F. G. (1943) *J. Amer. med. Ass.*, **121**, 1201.
FRANCIS, G. E., HAWKINS, J. D., and WORMALL, A. (1957) *Biochem. J.*, **65**, 560.
LAWS, J. O. (1952) *Brit. J. exp. Path.*, **33**, 354.
——, and WRIGHT, G. PAYLING (1952) *Brit. J. exp. Path.*, **33**, 343.
LITTLEWOOD, A. H. M., MANT, A. K., and WRIGHT, G. PAYLING (1954) *Lancet*, ii, 444.
MILLER, H. G., and STANTON, J. B. (1954) *Quart. J. Med.*, **23**, 1.
NOCARD, E. (1897) *Bull. Acad. Méd.*, 3rd. ser., **38**, 109.
RAMON, G., and FALCHETTI, E. (1935) *C.R. Soc. Biol., Paris*, **119**, 6.


**Dr. D. R. Laurence** (London):

*The Pharmacology of Tetanus*

In tetanus, convulsions, if uncontrolled and severe, may cause death. But patients with well-controlled convulsions often die, probably due to the action of tetanus toxin on the respiratory and cardiac centres in the brain-stem, and sometimes to over-enthusiastic use of drugs or to respiratory infection. The purpose of studying the control of tetanus muscle spasm with drugs is to assist in devising sufficiently simple regimes for the control of convulsions so that they can be used in places where tetanus is common. That there is no general agreement on which drug is the most effective anticonvulsant is shown by the polypharmacy commonly practised, and which is seen at its worst in some of the single case reports which are thickly scattered through the literature.

The principal reason for this polypharmacy is ignorance as to which drugs are capable of suppressing tetanus most effectively. Without this knowledge, and in the presence of the dramatic progress of a severe case, it is difficult to refrain from changing or adding to the treatment, for perhaps the next drug will be better than the last.

With this in mind, it was decided to undertake the measurement of the effect of drugs on experimental animal tetanus provided that it could be shown that animal and human tetanus responded similarly (subsequent experience has shown that animal and human tetanus do indeed respond to the same drugs at the same doses) and to seek a drug with ideal antitetanus properties. Such a drug should abolish tetanus convulsions without interfering with respiration in any way. It should not abolish consciousness, although suitable modification of consciousness would not be undesirable in this unpleasant disease.

Rabbits were chosen, injected with enough tetanus toxin to produce local hind-limb tetanus and electromyographs recorded in the manner described by Wright *et al.* (1952). It was soon found that the tetanus was too variable to give easily reproducible results and so a standard afferent stimulus was introduced. This gave a steady baseline from which predictable variations following drug administration occurred. The afferent stimulus eventually employed routinely was a tap delivered regularly by an electrically operated relay on the frame supporting the canvas sling supporting the rabbit.

For accurate quantitative measurements of drug effects a definite end-point was needed and this could not be conveniently obtained with the method as described. Therefore,

the voltages of the muscle activity were integrated to an arbitrary level and converted into units which could easily be counted. The apparatus now used is such that the amount of tetanus is indicated by the frequency of deflections on a moving paper, or the results can be presented in counts per minute. It is now possible to obtain accurate dose-response relationships with drugs and comparative bio-assays could be performed (Laurence and Webster, 1958).

Using this technique numerous compounds of various chemical groups were screened for antitetanus activity; they included barbiturates, mephenesin, benzimidazole derivatives, β-naphthoxyethanol and phenothiazines. The phenothiazines (chlorpromazine, acetylpromazine, promethazine) were much the most potent. Acetylpromazine is the most potent drug tested so far and arrangements are being made for it to receive preliminary clinical trial in Durban by Professor E. B. Adams. Animal experiments suggest that it may be an alternative to, rather than an improvement on, chlorpromazine.

If chlorpromazine or acetylpromazine are administered more frequently than about two-hourly the reduction of the tetanus may diminish and even disappear—i.e. tachyphylaxis occurs (Laurence and Webster, unpublished observations). This should be borne in mind when devising dosage schedules in man. Increasing the dose beyond a certain level, probably about 3–5 mg./kg., may not increase the antitetanus action. This is in agreement with the work of Rinaldi and Himwich (1955), showing that large doses of chlorpromazine may have the opposite effect from small doses on the brain-stem reticular formation.

Animal experiments having suggested that chlorpromazine had a powerful selective antitetanus effect in its own right, in 1955 it was used in a case of tetanus in a boy aged 2½ years (Kelly and Laurence, 1956). It was found that chlorpromazine used alone was capable of controlling severe tetanus spasms, although high dosage was required, but it was not without disadvantages and no opinion was expressed on its therapeutic value. This led to collaboration with Professor E. B. Adams of Durban, and we now think it possible to evaluate the place of the drug in clinical tetanus.

Local tetanus is very rare in man and generalized tetanus is usually either too variable or too dangerous for exact comparisons of drug effects. However, in Durban in 1956 a Bantu woman was admitted to the King Edward VIII Hospital with local tetanus in her legs. It was possible to carry out an investigation almost exactly comparable to those in rabbits already described and to confirm that similar drug responses could be obtained. By using regular dorsiflexion of the foot to stretch the gastrocnemius muscle, reproducible exacerbations of tetanus were elicited and recorded electromyographically. After twelve consecutive identical responses the administration of chlorpromazine abolished the tetanus. A crude dose-response relationship was obtained. Similar results were obtained with thiopentone. A dose-response relationship has also been obtained with chlorpromazine in tetanus by Barr (1958). In another study the tetanus was abolished by thiopentone (the patient became drowsy but remained conscious), and a conversation on a topic known to have emotional content for her was begun. The next muscle stretch produced a tetanus response similar to that before the drug. Further conversation of a sedative nature caused the response to disappear. This cycle was repeated three times with identical results (Laurence, 1957). It indicates the importance of mental rest in patients with tetanus. Patients in fear or pain may need more drug to control their convulsions than those mentally calm.

Until the appearance of acetylpromazine, chlorpromazine was the most potent phenothiazine drug against experimental tetanus. Chlorpromazine came into use in clinical tetanus soon after its introduction into anæsthetic practice (Mollaret *et al.*, 1952). It was given in combination with other drugs, empirically. Its remarkable antitetanus effect was not evident because of this and because of inadequate dosage. It has been thought that any effect chlorpromazine might have was due to potentiation of other drugs or to its mental tranquillizing effect.

Chlorpromazine is superior to mephenesin in that it is more potent and more convenient for intramuscular or intravenous injection. It is, however, more toxic, but not seriously so.

If the effect of a drug on experimental tetanus is unknown, then a physician may not feel able to use it boldly enough to obtain results. This was illustrated recently when an author wrote, after giving a modest dose of chlorpromazine daily to two cases, that the drug "seemed to have no specific effect on the disease" (Johnstone, 1958), and in the same issue of the journal, other workers reported that "large doses of chlorpromazine controlled the convulsions satisfactorily" in two severe cases of tetanus (Packard *et al.*, 1958).

An attempt has been made to show briefly how one aspect of the treatment of tetanus may be approached. It is obvious that the manifold problems of tetanus cannot be solved by experiments on rabbits, but there is reason to hope that the results of animal experiments, judiciously extended to man, may help in the choice of better therapeutic regimes. When preliminary studies have been done on man they should be followed by carefully designed

clinical trials on patients concurrently treated in different ways, for there can only be one criterion in evaluating treatments of tetanus—the demonstration of a significant reduction of mortality rate in trials designed to display the exact cause of any such change. Anything less than this is inconclusive.

REFERENCES

BARR, M. (1958) *Lancet*, i, 991.
JOHNSTONE, D. D. (1958) *Brit. med. J.*, i, 10.
KELLY, R. E., and LAURENCE, D. R. (1956) *Lancet*, i, 118.
LAURENCE, D. R. (1957) *Clin. Sci.*, **16**, 443.
——, and WEBSTER, R. A. (1958) *Brit. J. Pharmacol.*, **13**, 330, 334.
MOLLARET, P., BASTIN, R., POCIDALO, J. J., and BESANCON, F. (1952) *Bull. Soc. méd. Hôp. Paris*, **68**, 381.
PACKARD, R. S., CARTMILL, T. B., and HENRY, J. G. (1958) *Brit. med. J.*, i, 16.
RINALDI, F., and HIMWICH, H. E. (1955) *Dis. nerv. Syst.*, **16**, 3.
WRIGHT, E. A., MORGAN, R. S., and WRIGHT, G. PAYLING (1952) *Lancet*, ii, 316.

**Professor E. B. Adams** (Department of Medicine, University of Natal, Durban):

*Clinical Trials in Tetanus*

The clinical trials I am about to describe are the result of a combined effort between my team at the Medical School in Durban and Dr. Laurence at University College Hospital Medical School. The idea originated here in London when I heard him report on his work with chlorpromazine in experimental animals, and its successful use in a small boy with tetanus. Some of the properties of this drug suggested possible advantages over other forms of therapy. Its administration was simple and its toxicity low; and spasms could apparently be controlled without loss of consciousness. If proved to be of value, it would be a considerable advantage in those countries like my own where tetanus is common but the medical services often inadequate. In such places there are seldom sufficient numbers of trained medical personnel for the more complicated techniques like the use of neuromuscular blocking agents and positive pressure respiration.

In two years we have admitted 200 cases of tetanus to a small unit set aside for the purpose in King Edward VIII Hospital, Durban. All have been Africans or Indians. We have studied 171 of them in 2 clinical trials, and used other forms of therapy on the remainder without including them in the trials.

We have kept the design of our studies as simple as possible, our aim being to compare 2 different methods of treatment practised concurrently while keeping all other factors constant. We tried to eliminate the influence of variables over which one has no control by taking sufficiently large samples and allocating patients randomly to their treatment group. The most important of these variables appears to be the severity of the disease as judged by the length of the incubation period, the occurrence of reflex spasms, their frequency and severity, and the period which elapses between the first symptom of tetanus and the first reflex spasm (the "period of onset"). But the age of the patient, the site of the wound and the standard of nursing care also affect the outcome of treatment. By using sets of randomized envelopes provided by Dr. D. D. Reid of the Statistical Research Department, London School of Hygiene and Tropical Medicine, we have been able to allocate patients without conscious selection to treatment groups in which the only difference lies in the choice of drug to control reflex spasms. In this way we hoped to be able to assess the value of different methods of treatment, and in particular in these first 2 trials, to ascertain the value of chlorpromazine.

Of our 171 patients, 71 were infants in the neonatal period and I refer to them as "neonates". I have separated them from the remaining 100 children and adults whom I have grouped together as "non-neonates".

In the first trial, chlorpromazine was compared with barbiturates in the treatment of 75 patients, 31 of whom were neonates. In the second it was compared with a combination of barbiturate with chlorpromazine in the non-neonatal group, and with barbiturate and chloral hydrate together in the neonates. There were 96 patients in this second trial, and of these 40 were neonates. In all other respects we attempted to standardize treatment. As soon as the diagnosis of tetanus was confirmed, the next envelope was opened and the drug specified administered. An hour later neonatal cases were given 50,000 international units of antitetanus serum (A.T.S.) intramuscularly (i.m.). Children up to 10 years of age received twice this dose. Patients older than this were given 100,000 units i.m. and the same dose intravenously, provided no reaction followed within half an hour of a subcutaneous test dose (0·2 ml.). All were given long-acting penicillin as prophylaxis against chest infections, crystalline penicillin being substituted if abnormal chest signs

appeared. We attempted to feed all patients by mouth. Expressed breast milk was given to newborn infants through a nasal catheter, which was passed an hour after sedative treatment and left *in situ*. If oral feeding failed in the other patients, a nasal catheter was passed after adequate sedation. Only occasionally was intravenous feeding necessary.

*Control of Spasms*

Chlorpromazine dosage for *non-neonates* in the first trial was usually of the order of 100–150 mg. i.m. four- or six-hourly, and control of spasms was good. Occasionally when spasms were frequent and severe and their relief urgent, the intravenous route was used with good effect; and when oral feeding was impossible and there was difficulty in passing a tube, chlorpromazine by this route often proved a great help. Sometimes we had to give more than 1,000 mg. in twenty-four hours to control spasms. At these levels mental confusion followed in 2 patients whose subsequent deaths may have been due to overdosage, but apart from a tremor in another patient who recovered (on a lower dosage) toxic effects were inconspicuous. In the second trial we limited the total daily dose of chlorpromazine to 1,000 mg. When there was definite evidence of recovery, the dosage was reduced and the oral route used.

The barbiturates employed in both trials were phenobarbitone sodium, 200 mg. three- to six-hourly usually being required for control, and amylobarbitone sodium, 0·25 to 1·0 gram, either by the intramuscular or the intravenous route, when rapid sedation was necessary. In the second trial in which we used barbiturates and chlorpromazine in combination, we fixed the dosage of the latter at 300 mg. per day, varying the dose of phenobarbitone sodium; much smaller doses were necessary due to the potentiating effect chlorpromazine has on barbiturates.

As clinicians we have come to regard chlorpromazine as a better drug than the barbiturates for the control of spasms in *non-neonates*. Although both will control spasms, barbiturates sometimes have to be given in such high doses that consciousness is lost. This does not happen with chlorpromazine. On clinical grounds the combination of the two has much to recommend it.

In *neonates*, chlorpromazine dosage was correspondingly smaller, 25 mg. four- to six-hourly usually being given; initial doses of phenobarbitone sodium were of the order of 60 mg. six- to eight-hourly in the first trial, while in the second phenobarbitone was administered only during the first twenty-four hours, when the aim was to control spasms with as little barbiturate as possible, and not exceeding a total of 300 mg. Chloral hydrate was used thereafter, with a maximum dosage of 120 mg. four-hourly. In this difficult group of cases of tetanus control of spasms was often poor, and chlorpromazine appeared to be the inferior drug on clinical grounds. When large doses of any of these drugs were necessary to control repeated tetanic convulsions the infants often passed into a state of extreme flaccidity, without spasms, and would sometimes fluctuate between this condition and one of rigidity in which many reflex spasms would recur.

*Analysis of Results*

Although the diagnosis in all cases rested on the presence of typical muscular rigidity, and usually on the occurrence of reflex spasms as well, we regarded cases without the latter as "mild" no matter how severe their rigidity. Those patients with frequent reflex spasms we labelled as "severe", but when spasms were present only occasionally we classified the disease as "moderate". In the 100 cases of non-neonatal tetanus in these 2 trials, no deaths occurred among the 8 patients whose disease was "mild", only 2 died in the "moderate" group of whom there were 24, while there were 44 deaths among the 68 "severe" cases.

Looking at the results of treatment of non-neonates in both trials, it appears at first sight that chlorpromazine is somewhat better than barbiturate when these drugs are used alone (death-rates 43% and 52% respectively—*see* Table I), while chlorpromazine on its

TABLE I.—COMPARISON OF GROUPS: 1ST TRIAL—NON-NEONATES

| | | Chlorpromazine treated | Barbiturate treated |
|---|---|---|---|
| Number of cases | | 23 | 21 |
| Average age (years) | | 18 | 23 |
| Severity | severe | 15 | 13 |
| | moderate | 7 | 6 |
| | mild | 1 | 2 |
| Average incubation period (days) | | 15 | 11 |
| Average period of onset (hours) | | 32 | 31 |
| Mortality rate | | 43% | 52% |

TABLE II.—COMPARISON OF GROUPS: 2ND TRIAL—NON-NEONATES

| | Chlorpromazine treated | Mixture treated |
|---|---|---|
| Number of cases .. .. .. | 29 | 27 |
| Average age (years) .. .. | 13 | 21 |
| Severity { severe .. .. .. | 24 | 16 |
| Severity { moderate .. .. | 4 | 7 |
| Severity { mild .. .. .. | 1 | 4 |
| Average incubation period (days) .. | 13 | 11 |
| Average period of onset (hours) .. | 36 | 65 |
| Deaths .. .. .. .. | 15 | 9 |
| Overall mortality rate .. .. | 52% | 33% |
| Mortality rate among severe cases | 63% | 50% |

own is inferior to a mixture of this substance with phenobarbitone (death-rates 52% and 33% respectively—*see* Table II). But if we analyse the results critically, having regard in particular to the severity of the disease, the average incubation period and the mean period of onset of the various groups, we find that these differences are only apparent and not significant statistically. Reference to Tables I and II shows that the barbiturate-treated group in the first trial was weighted disadvantageously with regard to the mean incubation period (eleven days compared with fifteen); while in the second trial, the disease appeared to be more severe in those treated with chlorpromazine alone, for there was a higher proportion of severe cases, and the average period of onset was almost half of that in the mixture-treated group (thirty-six hours compared with sixty-five), although the average incubation period was somewhat longer (thirteen days compared with eleven). The mortality rates among severe cases in the second trial were 63% for those treated with chlorpromazine and 50% for those given chlorpromazine combined with barbiturates.

Treating the two neonatal groups similarly, no statistically significant difference is found to exist between the results of treatment with chlorpromazine and barbiturate in the first trial, nor between the mixture and chlorpromazine in the second, although superficially encouraging results followed the use of barbiturates alone. The mortality rates are very high in all 4 groups (Table III).

TABLE III.—COMPARISON OF GROUPS: NEONATES

| | Mortality rate |
|---|---|
| *1st Trial* | |
| Chlorpromazine treated | 93% |
| Barbiturate treated .. | 71% |
| *2nd Trial* | |
| Chlorpromazine treated | 95% |
| Mixture treated .. | 90% |

TABLE IV.—PRINCIPAL PROGNOSTIC CRITERIA: NON-NEONATES

| Treatment group | Mean period of onset (hours) in 87 cases | Mean incubation period (days) in 71 cases |
|---|---|---|
| *1st Trial* | | |
| Chlorpromazine—deaths .. | 23 | 15 |
| survivals .. | 41 | 15 |
| Barbiturate—deaths .. .. | 13 | 11 |
| survivals .. | 48 | 10 |
| *2nd Trial* | | |
| Chlorpromazine—deaths .. | 18 | 14 |
| survivals .. | 59 | 13 |
| Mixture—deaths .. .. .. | 26 | 7 |
| survivals .. .. | 84 | 14 |

If we analyse the records of the 100 patients in the 2 clinical trials among non-neonates, we find that the period of onset appears to be a more important prognostic criterion than the incubation period. The former was known in 87 cases and the latter in 71 (*see* Table IV). In both groups in the first trial and those who received chlorpromazine in the second, there was no difference between the mean incubation periods of those who died and those who survived, but the average in the mixture-treated group was appreciably lower among those who died (seven days compared with fourteen days). The average period of onset in all 4 treatment groups, however, was very much lower in those who succumbed than in the

survivors; and it is probably worth recording that the most favourable result of all occurred in the mixture-treated group of the second trial, with a death-rate of 33%, in whom the mean periods of onset of those who survived and of the group as a whole were by far the highest encountered (eighty-four and sixty-five hours respectively).

The relative importance of these 2 prognostic factors can be expressed in another way by comparing the death-rate of patients with incubation periods over nine days (30%) with the death-rate of those with shorter incubation periods (58%), and contrasting this difference with the much greater disparity between the death-rate in patients with periods of onset over forty-eight hours (9%) and that of those with periods of onset less than this (59%) (*see* Figs. 1 and 2).

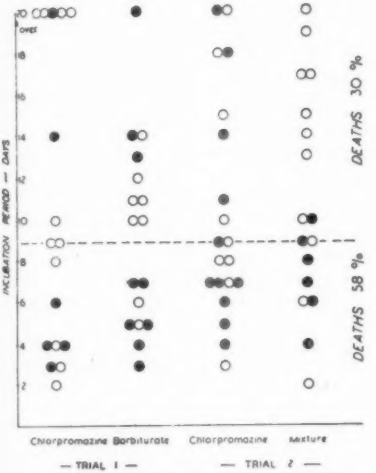



FIG. 1.—Prognosis related to incubation period — non-neonates. ○ = Survivors: ● = Deaths.

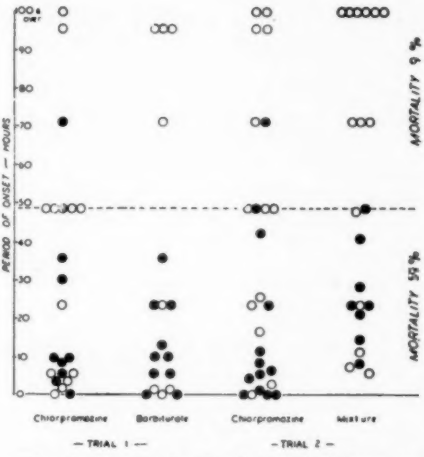



FIG. 2.—Prognosis related to period of onset—non-neonates. ○ = Survivors: ● = Deaths.

*Causes of Death*

It is difficult to be sure what causes death in tetanus and I would find it impossible to classify the causes in our cases in the way that was done by Creech *et al.* (1957). Pneumonia accounted for death in about half of their 116 patients who died between 1943 and 1949, and for a third of the 55 deaths between 1950 and 1956. Other respiratory causes such as atelectasis, aspiration, pulmonary œdema and asphyxiation brought the respiratory causes of death up to 81% and 70% respectively, septicæmia, convulsions, cardiac arrest and unknown causes comprising the remainder.

Autopsies on our cases seldom showed an adequate cause of death. Varying degrees of pneumonia were present in a quarter, and small areas of collapse or some pulmonary congestion and œdema were sometimes seen, but often the changes were not striking. In our second trial we examined the lungs histologically in 23 out of the 24 fatal cases among non-neonates and found 6 with pneumonia (27%), 3 in each treatment group. Among the neonates in this trial the lungs were examined histologically in 31 of the 34 who went to necropsy. Pneumonia was present in 8 (26%), 6 in the mixture group.

I doubt whether exhaustion from spasms and muscular rigidity often results in death in non-neonates, because we can usually control these manifestations of the disease; but exhaustion may be important in neonates in whom spasms are more difficult to control. In this group oversedation is all too easy to achieve and probably causes death in some cases. In a few patients laryngeal spasms occur and may be fatal, although prompt intravenous chlorpromazine has sometimes proved successful. These laryngeal spasms together with occasional unexplained sudden deaths in other patients, and the rather more frequent apnœic attacks in neonates, suggest that tetanus intoxication of the medullary centres should certainly be included among the causes of death in this disease. It may even be the most important cause.

*The Need for Clinical Trials in Tetanus*

Our two trials have shown that no definite reduction of the mortality rate has followed the introduction of chlorpromazine for the treatment of tetanus when compared with sedation methods which have often been used before.

So far no one form of treatment of this disease has been proved to be really effective. Much of the literature consists of isolated reports, and a large variety of methods of treatment has been tried, often with claims of efficacy which are unfounded if the prognostic features of the cases upon which they were tried are carefully weighed up; indeed many reports fail to include details of the various prognostic criteria already discussed. I hope I have succeeded in drawing attention once again to their importance. This has often been done in the past, as in the report of Cole (1940), who stressed in particular the fact that the period of onset is probably the best index to use when making comparisons of methods of treatment. I have already illustrated the important relationship of period of onset in particular to death-rate, but it is perhaps worth remarking that we predicted recovery in one or our neonatal patients in whom the period of onset had been very long—a somewhat hazardous procedure in a disease which usually carried a mortality rate of about 90%.

Reviewing their experience with 558 cases of tetanus over a fourteen-year period in New Orleans, Creech *et al.* (1957) concluded that none of the newer methods could justifiably be claimed to be a therapeutic advance. They showed that there had been a steady decline in the mortality rate for the disease at their hospital over the past fifty years. They criticized reports of small numbers of cases with no deaths, such as that of Forbes and Auld (1955), who had 15 consecutive survivors, for they were able to cite 19 successive recoveries from the disease during one year, when, however, the overall mortality rate remained unchanged; and it is probably worth pointing out that we encountered 10 successive cases in our second trial with only 1 death, and 14 with only 2. There have been many reports of large series of cases treated by various methods, particularly from the United States, but while claims for this or that regime are often made, none will stand critical review, for there have been no properly conducted clinical trials.

Our trials show that reasonable results can be obtained with simple methods of treatment, except in neonates. On the basis of our experience so far I would recommend the use of a combination of chlorpromazine and phenobarbitone in doses similar to those we used in the second trial, as well as a large initial dose of A.T.S. and prophylactic penicillin. Good nursing is essential. Oral secretions should be watched, and removed by suction when excessive. A majority of patients on chlorpromazine can be fed orally. If tube feeding is necessary but the passage of the tube proves difficult or provokes spasms, intravenous chlorpromazine can be used; and it is also often effective in the treatment of laryngeal spasms. Deaths in tetanus usually only occur in patients with severe reflex spasms, and overtreating milder cases should be avoided.

We now propose to try to evaluate the role of tracheotomy in treatment by conducting a new trial on patients classified as severe cases of tetanus. All will be treated with the mixture of chlorpromazine and barbiturate, while one group, selected by the same method of random sampling, will be subjected to tracheotomy. Later we hope to study the use of muscle relaxants and positive pressure respiration by a similar technique.

*Acknowledgments.*—Thanks are due to the Wellcome Trust who have generously supported this work, to Dr. S. Disler, Medical Superintendent, King Edward VIII Hospital, Durban, for facilities, to the staff of the Department of Pathology, University of Natal, and to Drs. E. Berman, J. Scragg and R. Wright for their clinical assistance.

REFERENCES

COLE, L. (1940) *Lancet*, i, 164.
CREECH, O., GLOVER, A., and OCHSNER, A. (1957) *Ann. Surg.*, **146**, 369.
FORBES, G. B., and AULD, M. (1955) *Amer. J. Med.*, **18**, 947.

**Dr. A. Crampton Smith** (Nuffield Department of Anæsthetics, Radcliffe Infirmary, Oxford):

*The Treatment of Severe Tetanus by Paralysing Drugs and Intermittent Pressure Respiration*

Since 1953 I have been associated with Dr. Ritchie Russell and Dr. John Spalding in the treatment of paralysed patients by tracheotomy and intermittent pressure respiration. We have treated 7 patients with very severe tetanus by paralysing them completely with curare and our experience leads us to believe that there is a group of patients most severely affected by tetanus to whom this form of treatment offers the only chance of survival.

Tetanus carries a high mortality, but this mortality can be masked by various influences, not least of these the fact that tetanus is in some countries relatively uncommon, and that success in a few consecutive cases may be wrongly attributed to a new method.

Creech *et al.* (1957) of the Charity Hospital, New Orleans, commenting on a series of 15 consecutive recoveries reported by other workers remarked that in 1949 they observed 19 consecutive recoveries, but their overall mortality in that year was 42%.

The same authors use a graph of the results of the treatment of tetanus in their hospital since 1906 to show that the introduction of new forms of treatment such as tracheotomy, gastrostomy, antibiotics and muscle relaxants have had little dramatic effect on the general downward trend of mortality which they attribute to improved nursing care and supportive therapy. This improvement is gratifying but if one selects the most severely affected patients, the results of treatment leave little room for complacency.

Criteria of severity in tetanus are not finally established, even Cole's classification (Knott and Cole, 1952) being perhaps not entirely satisfactory, but there is general agreement that an incubation period of about a week and an onset period—the time between the first symptom and the first generalized spasm—of under forty-eight hours are of very grave prognostic significance.

For instance, in 100 cases reported from Nigeria (Johnstone, 1958) the overall mortality was 50%, but in those patients with an incubation period of less than nine days and an onset period of under forty-eight hours the mortality was 79%. In a Mayo Clinic symposium on tetanus (Christensen and Thurber, 1957), of those patients with an incubation period of four to six days inclusive 72% died, and in those with a short onset period 82% died, and of 13 patients with what is described as grade IV tetanus the authors say: "The course of the disease in this group was always rapidly progressive, extremely severe and unrelenting finally culminating in death forty-eight to seventy-two hours after the onset."

Even in a series of 236 cases with the low overall mortality of 18·2% reported by Veronesi (1956) the group with an onset period of under forty-eight hours had a mortality of 44%, and it is in this most severe group that we are particularly interested.

The use of curare in tetanus has a long history, since 1860, and indeed it would be surprising if this were not so, the formidable capacity for muscle relaxation of this drug inevitably leading to its consideration as a possible cure.

The discovery of a drug to relieve the spasms of tetanus without any side-effects will always be the pharmacological aim in this disease. Curare is certainly not this drug, and a lack of appreciation of the potentialities and also of the limitations of this drug has led to its unpopularity with some workers, especially in America.

The New Orleans opinion of curare, for instance, is based on 5 cases treated with little success and reported by Adriani and Ochsner, again from the Charity Hospital, in 1947. They state: "A graded response could not be obtained, and the amount of drug necessary to obtain relaxation caused complete curarization."

As late as 1956, in the review previously mentioned, Veronesi writes: "Some cases do not respond satisfactorily to any muscle relaxant drug. Such cases present the most difficult problem—namely to obtain relaxation without paralysis."

We believe that there is a small group of patients whose spasms cannot, in the present state of knowledge, be controlled except by paralysis with curare or other equally powerful relaxant, but the amount of relaxant necessary to control these spasms will paralyse all the patient's voluntary muscles, including those of swallowing and of respiration. This situation must be accepted, and artificial respiration regarded as inevitable in patients with tetanus treated with curare.

In 1952 an epidemic of poliomyelitis of considerable magnitude occurred in Copenhagen. During this epidemic, the method of treatment of paralysed patients by tracheotomy, cuffed rubber tracheotomy tube and artificial respiration through the tube was instituted, and has now come to be used in a variety of circumstances.

In October 1953, the Danish workers published details of a case of severe tetanus in which the spasms of tetanus had been abolished by paralysing the patient with curare and by maintaining respiration by intermittent pressure respiration through a cuffed tracheotomy tube (Bjornboe *et al.*, 1953).

In the respiration unit at Oxford we have treated a small group of patients with very severe tetanus—seven in all—by this method, with four recoveries, and as is apparently invariably the case in tetanus the patients who recovered had no sequelæ.

When the decision to apply this form of therapy has been taken, and it may be taken at a considerable distance from the place where the patient is to be treated, the patient is anæsthetized, paralysed with curare or other relaxant and a cuffed endotracheal tube is inserted through the mouth. He is then transported, being ventilated manually by an anæsthetist, and in the hospital where he is to be treated a cuffed tracheotomy tube is placed in the trachea through a tracheotomy, and intermittent pressure respiration is applied by a suitable machine.

The fact that the patient is completely paralysed complicates his treatment. He cannot move, breathe or eat and—probably most difficult of all—he cannot communicate.

He is ventilated, and suitably ventilated. He is fed by a gastric tube, and his electrolyte balance is investigated and controlled. His urine is collected and its specific gravity and content explored. He is turned from side to side every two hours to avoid chest complications and pressure sores. Secretions are aspirated from his trachea at frequent intervals. Chest radiographs are taken and frequent observations of pulse-rate, blood pressure, temperature and respiratory minute volume are recorded.

The nurse in attendance injects curare intramuscularly with hyaluronidase whenever the patient moves.

The complications of his disease must be treated, hyperpyrexia and peripheral circulatory failure being in our experience the most serious.

Although this regime is complicated, we do not believe that in reasonable circumstances it carries a high mortality. Table I shows the results of treatment in various diseases at

TABLE I.—PATIENTS TREATED WITH INTERMITTENT POSITIVE PRESSURE RESPIRATION IN THE UNITED OXFORD HOSPITALS, JUNE 1953–FEBRUARY 1958

| | Treated | Deaths | Recovered Partially | Recovered Fully |
|---|---|---|---|---|
| Poliomyelitis .. .. .. .. | 32 | 7 | 25 | 0 |
| Polyneuritis .. .. .. .. .. | 10 | 1 | 2 | 7 |
| Tetanus .. .. .. .. .. | 7 | 3 | 0 | 4 |
| Barbiturate poisoning .. .. .. | 4 | 1 | 0 | 3 |
| Myasthenia gravis .. .. .. | 2 | 0 | 2 | 0 |
| Post-thoracotomy (malignant growths or tuberculosis) .. .. .. | 4 | 4 | 0 | 0 |
| | | | 29 | 14 |
| Total | 59 | 16 | 43 | |

Oxford, and in the conditions where the patient has a reasonable expectation of survival, the mortality is respectable.

What is probably more important is that Table I represents more than 100,000 hours of treatment by the method described.

To summarize, patients with severe tetanic spasms will die if their spasms are not controlled. If curare or similar powerful relaxant is necessary to control severe spasms, sufficient should be given to paralyse the patient completely and artificial respiration must therefore be used as well.

It would be foolish to deny that this form of treatment is expensive, especially in nursing care, and may be economically impossible not only in other countries, but even in our own country in hospitals where the available nursing staff is already working to the limit of its capacity.

Centres exist in many regions where this and other forms of treatment of tetanus are available, and we feel that it should be recognized that patients with tetanus can be transported even when their disease has developed to the point where severe opisthotonic spasms are occurring.

Tetanus is already an uncommon disease and with the spread of prophylactic immunization will become even more rarely encountered. We have, in common with Professor Adams and Dr. Laurence, a feeling that the present haphazard approach to the many forms of therapy available will delay the reduction of the mortality from tetanus to the minimum possible.

Perhaps there is room for an approach to tetanus on a national level, not only in respect of prophylaxis, but also in respect of therapy.

## REFERENCES

ADRIANI, J., and OCHSNER, A. (1947) *Surgery*, **22**, 509.

BJORNBOE, M., IBSEN, B., and JOHNSEN, S. (1953) *Ugeskr. Læg.*, **115**, 1535.

CHRISTENSEN, N. A., and THURBER, D. L. (1957) *Proc. Mayo Clin.*, **32**, 146.

CREECH, O., GLOVER, A., and OCHSNER, A. (1957) *Ann. Surg.*, **146**, 369.

JOHNSTONE, D. D. (1958) *Brit. med. J.*, i, 12.

KNOTT, F. A., and COLE, L. (1952) British Encyclopædia of Medical Practice. 2nd edit. London; **12**, 40.

VERONESI, R. (1956) *Amer. J. med. Sci.*, **232**, 629.

# Section of Epidemiology and Preventive Medicine

President—IAN TAYLOR, M.D., M.R.C.P., D.P.H.

[*May* 16, 1958]

JOINT MEETING WITH THE FEVER GROUP OF THE SOCIETY OF MEDICAL OFFICERS OF HEALTH

## SYMPOSIUM ON THE ASIAN INFLUENZA EPIDEMIC, 1957

**Dr. A. M.-M. Payne** (Section of Endemo-epidemic Diseases, World Health Organization, Geneva):

### *Some Aspects of the Epidemiology of the* 1957 *Influenza Pandemic*

The 1957 pandemic of influenza is the first that it has been possible to study using modern virological techniques in an almost world-wide network of laboratories which had been organized by the World Health Organization with just such an eventuality in mind. It was almost ironical therefore that the epidemic should originate in an area not covered by the programme. The first reports to reach WHO were from Singapore early in May to the effect that an extensive outbreak of influenza was occurring and that it appeared to have been introduced from Hong Kong. Later, information was received that the epidemic began in continental China about the third week in February and according to Chu (1958) it originated in Kweichow Province between Kweiyang and Kutsing which is in Yunan Province. In early March the outbreak had spread to Yunan Province and by the middle of March it had spread all over China. The virus was first isolated in Chanchung by Chu *et al.* (1957) and in Peking by Tang and Liang (1957) and it is clear that they recognized most of the important features of the virus which have since been described elsewhere. It is unfortunate that this information did not reach the rest of the world until the epidemic was already spreading widely. If it had we should have had two more months in which to prepare. However, in the event, virus was isolated by Hale (Lim *et al.*, 1957) in Singapore, and by a United States Army Laboratory in Japan, early in May (Meyer *et al.*, 1957) and was identified as a new variant of virus A at the World Influenza Centre in London, at the Walter Reed Army Institute for Medical Research in Washington, and at the Walter and Eliza Hall Institute in Melbourne, the news reaching WHO on May 23 and being broadcast in WHO's world-wide epidemiological broadcasts on the following day.

The epidemic spread from continental China to Hong Kong in the third week of April, appearing first among persons coming from the mainland. By the end of April it had already spread to Singapore and Taiwan, and in May it involved extensive areas of Indonesia, the Indo-Chinese peninsula, the Philippines and Japan. Fig. 1 shows the rate of spread of the epidemic from the reported origin in southern continental China. The figures in the black circles show the month in which the first cases occurred according to the information so far available. It may be that when final reports are received some changes will be necessary. Most circular spots represent the first outbreaks but some represent the first reported infections, some of which did not result in epidemics but represent the seeding of the virus in the population. The square spots in Japan, the U.S.S.R., the Netherlands, for example, indicate later outbreaks which were always extensive.

In the month of May there were two introductions into Australia by persons coming from Singapore, one in Cairns and the other in Melbourne; the former by the crew of a ship and the latter by air passengers. Neither introduction resulted in an immediate outbreak in the general population though there was a small epidemic of about 200 cases in a camp in a rural area in Victoria. Towards the end of May and in June the epidemic spread very rapidly through south-east Asia involving Burma, India, Pakistan, the Persian Gulf, and reaching Aden. Outbreaks began to occur in Australia and local introductions were noted in the Netherlands, in the United Kingdom and in the United States of America. During this period spread was also taking place by the land route from China. Local outbreaks occurred in some cities of the central Asian Republics, in the Ural area, along the Siberian main railway, and in Moscow and Leningrad. In the latter cities the first cases were detected in the middle of May, but definite outbreaks did not occur until June. Outbreaks also occurred in Czechoslovakia and Romania.

In July the epidemic wave had reached the Near East, South Africa, New Zealand, and several Pacific coast South American States. In August and September spread continued and by the end of that month it was evident that practically the whole inhabited world had

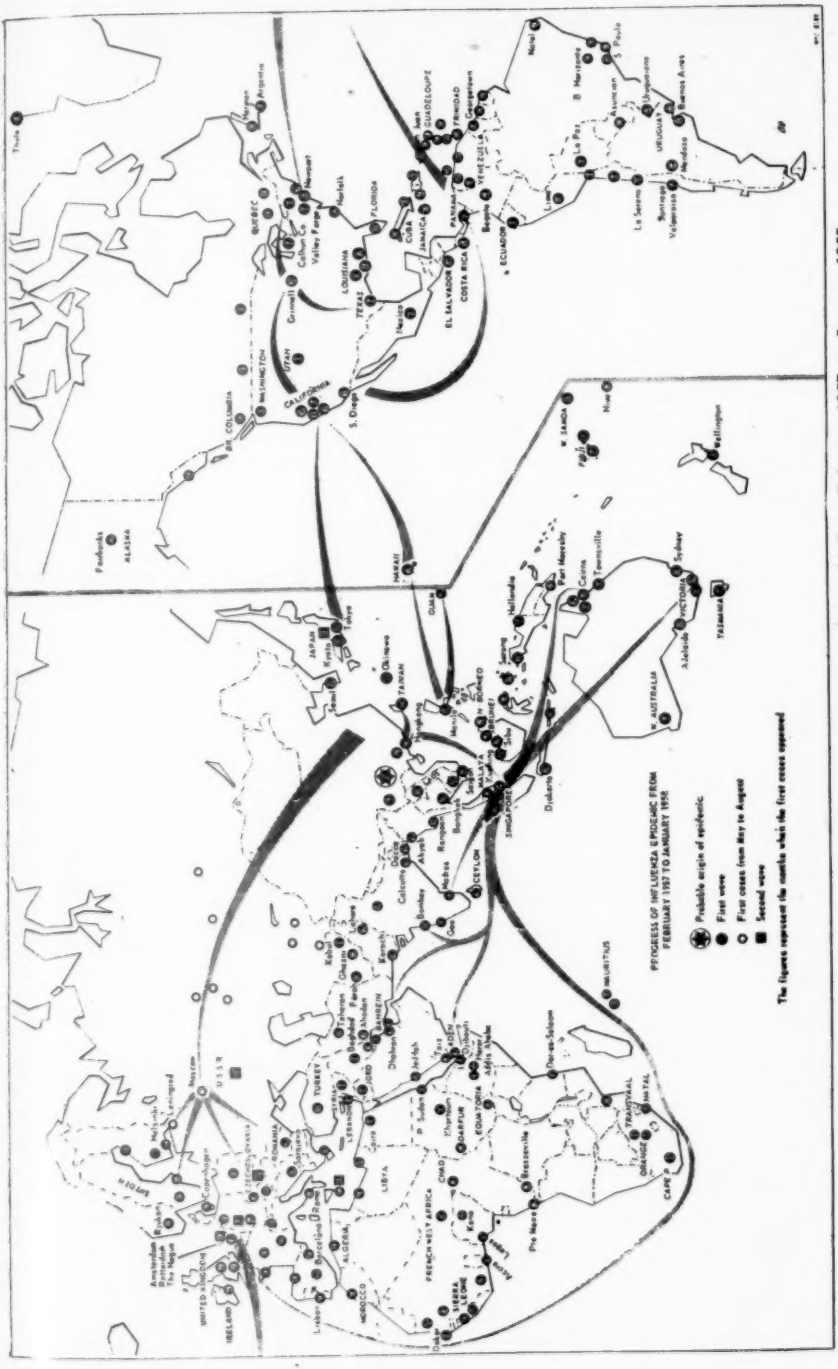
been infected, or at least seeded with the virus, except perhaps some isolated communities. In the southern hemisphere extensive epidemics were occurring although in Australia they were not perhaps as large as had been anticipated but extended over a longer period. In the northern hemisphere these did not begin until the end of September and October. In October-November some countries, notably Japan, parts of the U.S.S.R. and Czechoslovakia, began to experience a second wave of infection. Towards the end of November and in December major epidemics were ending in almost all countries. In the first months of 1958 no large outbreaks were reported but many countries experienced an unusually high incidence of sporadic influenza with some local outbreaks and the morbidity and mortality due to respiratory disease was in some countries considerably above the average. I shall return to this later.

This rather brief account of the spread of the pandemic shows that a new virus apparently originating in a single area in China involved the whole world in the space of about seven months.[1] This may be attributed to the high infectivity of the virus and the fact that few persons had had previous experience of this antigenic type and could present no obstacle to its multiplication and spread.

The speed of the spread of this pandemic does not seem to have been faster than previous pandemics. The pandemics of 1789, 1889–90, and 1918–19 all seem to have spread with remarkable speed and the first of these occurred at a time when international transport was very slow. In neither of the last two could travel by air have played any part and yet their spread seems to have been just as rapid. Of course, we do not know the identity of the ætiological agents of these pandemics. For example, we do not know whether the virus responsible for the mild but extensive outbreaks in the spring of 1918 was the same as that responsible for the severe outbreaks which started in the autumn. This may be compared with the experience in Japan last year. An extensive outbreak due to the Dutch 1956 strains occurred in January–March, followed by the Asian outbreak in May–June, and again in October–November. Without laboratory tests it would have been impossible to say that the first two epidemics were due to different viruses and it might have been concluded that Japan had three waves of the same infection in a single year. If the two 1918 waves were due to the same virus it is possible to explain the simultaneous appearance of the second severe wave in widely separated parts of the world by assuming that the virus was widely seeded during the first mild wave and that some as yet unidentified factor was responsible for exciting the appearance of the severe form of the disease at the same time in extensive geographical areas. In 1957 the rapid spread through the tropics seems to have been due to relatively massive introduction of the infection into countries through the ports following outbreaks on ships arriving there. Introduction by aircraft seems to have been much less effective in starting an immediate outbreak although it may well have been an important mechansm of seeding the virus throughout the world to await the appearance of an unknown exciting factor before causing widespread outbreaks later in the year. Isolated introductions by aircraft were detected in the United Kingdom, the Netherlands, and Australia, but rarely as far as I know in the United States of America. In the Netherlands (Mulder, 1957), for example, the first Asian virus isolated in Western Europe reported to WHO was from an air passenger from Djakarta who arrived on June 4. The next case detected in the country was in a girls' school in Bussum near Amsterdam on June 16, but no contact could be established with the previous case. There was also a laboratory infection in Leiden and this was apparently the only secondary infection resulting from the passenger from Djakarta indirectly via a ferret. It seems more probable that the infection was introduced into the country from outbreaks in ships arriving at Rotterdam and the Hague, and it spread widely in July in camps of Indonesians in different parts of the country with little spread in the general population at that time.

In the United States of America the first outbreak was surprisingly on ships at Newport on the east coast, no contact with Asia being detected (Langmuir *et al.*, 1958). However, it seems that seeding of the virus throughout the country followed outbreaks in military and civilian groups in California, the spread being traced rather clearly as taking place through students, scouts and similar groups attending conferences or jamborees where they were infected and carried the infection to different parts of the country when they dispersed. A ship-borne introduction was also noted in Chile. A U.S. Navy vessel arrived in Valparaiso from an American port where an outbreak of influenza had occurred. Influenza-like illness had occurred on board and a few days after the visit an extensive outbreak began in the town and involved the rest of the country. The infection was brought back to the United States to Miami by the crew of a Chilean aeroplane but I do not know whether this "retaliation" caused any spread.

[1]A more detailed account may be found in the WHO Weekly Epidemiological Record, 1957, Nos. 19–52, and 1958, Nos. 1–13.


PROGRESS OF INFLUENZA EPIDEMIC FROM FEBRUARY 1957 TO JANUARY 1958
Probable origin of epidemic
First wave
First cases from May to August
Second wave
The figures represent the months when the first cases appeared
Truro
Fairbanks
ALASKA
Harper
Argentia
Goose
Churchill
Winnipeg
Thunder Bay
Sault Ste Marie
Toronto
Ottawa
Montreal
Quebec
Fredericton
Halifax
Charlottetown
Gander
Stephenville

In both Europe and North America the start of the main outbreak coincided with opening of schools where outbreaks were first observed, afterwards spreading via siblings and parents to other schools, factories, &c., and to the general population.

In both South Africa and India and in some other countries an attempt was made to delay introduction of the infection by quarantine measures against ships and aircraft. In most countries including India this was ineffective. For example, the disease appeared in epidemic form in Madras and Bombay towards the end of May. In South Africa, on the other hand, the impression was gained that these measures may have been partially effective since the epidemic did not commence until July. In Israel, isolated from neighbouring countries by the political situation, the epidemic did not begin until mid-September, a delay of two months.

In the U.S.S.R. the infection seemed to travel along the railway across Siberia, but it is not possible to assess the importance of air travel since there is a good deal of movement along the air route from Peking to Moscow and on to Prague which is an important air centre.

It was notable that in many countries the first outbreaks occurred in crowded communities, schools, camps and institutions, and many outbreaks under the crowded conditions on ships were reported. It was evident that crowding played a big role in building up a mass of infection from which it spread to less crowded population groups. This was observed early in Singapore and Malaya as reported by Lim *et al.* (1957) and Gordon Smith *et al.* (1957). The attack rates were at first so strikingly different in Europeans and the indigenous populations as to lead to a suspicion that there might be a difference in racial susceptibility. However, this difference could equally be attributed to the difference in living conditions and later observations did not support the view that there is any difference in susceptibility.

As is well known morbidity data regarding the incidence of influenza is highly unreliable so that estimates of the overall incidence in a country can only be very rough. Most estimates have been based on observations in cities. These have varied up to 70% attack rates. Better estimates can be obtained by studies of sample groups and also by serological surveys. In some countries studies of absenteeism in industry and in schools (where up to 80% attack rates have been observed) or of health insurance claims have been useful. In Singapore, Hale estimated the attack rate among civilian dock workers as about 30%. An estimate among city employees in Manila corrected for the age distribution of the population was 23% (Tayback and Reyes, 1957). Attack rates on ships have varied considerably and have often been higher among crews than among passengers. One such incident for example gave an attack rate of 30% for the crew and only 10% for the passengers. It is tempting to attribute this as well as the high rate in residential schools to the effect of crowding and close contact which I have already mentioned. In Bombay a random survey by Patel and Rao (1957) gave an overall attack rate of 42%, but in different parts of the city it varied from 11% to 75%. In several tropical countries the attack rates in rural areas have been thought to be much lower but I do not know what reliance can be placed on these since in many such areas health services are poorly developed. Great variation in the attack rate in different areas and even among different groups in the same town was found by Fukumi (1957) in Japan. He studied random samples of sera, 30 specimens being collected from each of 12 health centres in 14 prefectures, a total of 5,000 sera. The range of positive findings in the different health centres according to the hæmagglutination inhibition test was from 0 to 93%, with an overall average of about 40%. Even in the same prefecture great variations were found. This work was carried out at the end of July after the first wave. It was notable that the second wave in November affected much more severely those areas which had been lightly affected during the summer. A similar finding was also made in the U.S.S.R. It seemed therefore that a degree of immunity resulted from an attack. I have no reports of second attacks, both attacks being confirmed by virus isolation, but on serological grounds second attacks have been detected with an estimated frequency of less than 4% in Japan and about 12% during the second epidemic in Leningrad. There, on the basis of serology the attack rate was estimated as 25% during the first wave and 30% during the second (Smorodintsev, 1958).

The age distribution of cases has been similar in most countries, very young children and persons over 40 being rather less frequently affected. For example, in Bombay, 9% of all cases occurred under the age of 5 and 15% over the age of 40, and 76% between these ages. In the United States of America the age group 5–19 had the highest incidence and there was a very low incidence over the age of 65. In Chile only 3% of cases occurred over the age of 60, and in the Philippines only 2·3%. Relative sparing of the older age groups has been observed everywhere and I will return to the possible explanations of this later.

In contrast to the attack rate the mortality has been highest in the very young and in the elderly, though there has been some variation in this. In Leningrad, 38% of deaths were in the first two years of life and 22% over the age of 45. In Manila, 53% of deaths were under

the age of 4 years and only 11% over the age of 50, whereas in Santiago 22% were under the age of 1 year and 55% over the age of 55. In the Netherlands approximately 40% of deaths were in persons over the age of 60 and 10% under the age of 4. In that country there was a striking excess of deaths in young adult females. Some reports I have received have suggested that during part of the epidemic in some countries there was a tendency for adolescents and young adults to be more severely affected than at other times during the epidemic but more detailed figures are necessary before this can be assessed. In Tokyo the age distribution of deaths attributed to influenza was the same in the two waves, more than half the deaths being over the age of 50, and about 20% under the age of 10, most of these being in infants. In the Philippines the overall mortality from all causes was double the usual figure during the epidemic wave and this was also found in many other countries. Influenza must have been a contributory factor in a very considerable number of deaths even though the direct mortality rate was generally low. It is difficult to make any reliable estimate of the actual mortality rate. Estimates varying from 1 in 300 cases to 1 in 10,000 have been made, somewhere between 1 in 2,000 to 1 in 6,000 being most frequent.

Most deaths were as usual due to bacterial pneumonia, staphylococcal infections being particularly troublesome in most countries. The proportion of strains resistant to antibiotics was relatively high in fatal cases compared with those isolated from cases that recovered. In these strains resistance was common to penicillin and streptomycin, less common but quite frequent to Aureomycin and Terramycin, and least common to erythromycin (Hers *et al.*, 1957). There were, however, a not inconsiderable number of early deaths from hæmorrhagic pneumonia, virus being isolated readily from the lung and with no evidence of secondary bacterial infection. These cases occurred sporadically and not in groups as would have been expected if the virus had developed increased pneumotropism. Attempts at primary isolation of virus in mice also failed to reveal any such change. These cases were commonest in young persons, and when they occurred in older persons there was generally some other pathological condition. Persons with pre-existing heart disease, mitral stenosis for example, seemed particularly liable to develop this type of pneumonia and there was some indication that pregnant women were also at some increased risk. However, more complete data are needed to determine whether these impressions are really significant. It is not possible to say why some apparently healthy individuals developed the severe form of the disease. The absence of any increased pathogenicity of the virus for the mouse lung might be interpreted as favouring individual susceptibility as the most important factor rather than any change in the virus. This is perhaps also supported by the sporadic occurrence of these cases. It is, however, evident that we need better methods of estimating the pneumotropic properties of the influenza virus.

The clinical picture generally does not appear to have differed significantly from influenza due to other strains prevalent in recent years. From some countries reports were received of symptoms suggesting involvement of the central nervous system but I am inclined to think that these were toxic symptoms rather than due to direct involvement of the central nervous system by the virus. In young children an unusual biphasic form of illness was observed in some countries, including the U.S.S.R. where it was studied by Zhdanov and Ritova (1958). An apparently normal recovery about the third day of illness was sometimes followed by a relapse on the fifth day, virus being readily isolated from the throat for several days longer. These relapses were not associated with bacterial infection and did not respond to antibiotics. A number of them proved fatal.

To return to the epidemiology of the disease, an extremely interesting observation was made by Mulder (1957) who found that some persons over the age of 70 had hæmagglutination-inhibiting antibodies to the Asian virus. This was confirmed in some other countries before the arrival of the pandemic wave but could not be confirmed everywhere (Davenport, 1958). The problem is to interpret this finding and the bearing it may have on the persistence of strains of influenza A virus in nature and the emergence of new antigenic variants. An attractive interpretation of Mulder's finding is that the Asian virus may be related to the virus responsible for the pandemic of 1889–90 since antibody is present in some persons who lived through that period. If that is correct it raises the question as to where the virus has persisted all this time. Shope's (1958) work on swine influenza and serological investigations such as that by Davenport *et al.* (1953), suggesting that a virus antigenically related to the swine virus was prevalent in man about the time of the 1918 pandemic, raise the possibility that there may be an animal reservoir for human strains of influenza A virus. Several types of influenza A virus do in fact cause natural disease in animals; in addition to swine influenza there are epizootics in horses due to influenza virus A which have occurred recently in Czechoslovakia and Scandinavia, fowl pest is due to a virus belonging to the A group, and there is also a disease of ducks due to an A group virus. Some support for this speculation was given by a report of the isolation of the Asian virus from a pneumonic patch in a pig's lung in China last summer. An epizootic in horses occurred in Kharkov at the time of the

human epidemic and is reported to have been due to the Asian virus. Confirmation of these reports is awaited. It was clear that the 1957 pandemic presented a unique opportunity of testing this hypothesis. WHO therefore arranged for the collection of sera from pigs and horses and some other domestic animals in 25 countries before the pandemic wave reached them, and this is being followed by the collection of further sera, as far as possible from the same animals, after the pandemic. These will be examined for hæmagglutination-inhibiting and complement-fixing antibodies to the Asian, swine and other influenza A viruses. This is a first step in the reinvestigation of the problem of animal influenza and its possible relation to human disease. No results are yet available.

Another interpretation of Mulder's findings is based on a theory which has been well set out by Isaacs *et al.* (1954), that influenza viruses contain many different influenza A antigens but that most of these are masked and only the dominant antigens on the surface of the virus particle can be detected by the methods usually employed. These masked antigens may be considered to be inside the virus particle and unable normally to stimulate the production of antibody. When mutations occur a rearrangement of antigens may take place and the masked antigens may replace the previously dominant surface antigens. This attractive theory would certainly explain many observations on the epidemiology of influenza. Additional support has recently been provided by observations by Fabiyi (1958) in Henle's laboratory. Using a highly strain-specific virus (V) antigen freed from the soluble (S) antigen he showed, in the C.F. test, that there were cross-reactions, which were usually reciprocal, between groups of influenza A viruses previously considered unrelated except by the soluble antigen. For example he detected the WS antigen in the Asian virus and the Asian antigen in A strains isolated in Philadelphia in 1951 and 1953. The occasional lack of reciprocity in these tests is explained by postulating that the antigens may be present in minimal amounts or may be masked. He has studied the anti-V response in cases of influenza and has found rises not only to the epidemic strain but also to other V antigens. In general it was found that the older the individual the broader the response. This does not support Davenport's theory of "original antigenic sin" (Davenport and Hennessy, 1957) according to which the first exposure to the virus determines the major response to subsequent infection with any type A virus since it was found that many young individuals, born long after strains of swine virus and the PR8 group had disappeared from circulation, showed antibody response to the V antigens of those viruses. Antibodies to the Asian V antigen were demonstrated in sera collected from various age groups before the variant appeared. It was felt that the breadth of the spectrum of anti-V responses could be interpreted on the basis of multiplicity of exposures to influenza viruses rather than on the specificity of the original infection. Minimal antigenic components which were never dominant in strains responsible for past infections may nevertheless condition individuals to respond ultimately with detectable antibody to these antigens. He has demonstrated this broadening of response by repeated infection of guinea-pigs causing the appearance of antigens dominant in strains isolated years before or after the strain used for the infection. He concluded that many if not all of the past and future antigens are represented in nearly every strain of influenza A virus. Any one antigen may assume dominance in a given year. Those present in minimal amounts may only become detectable by their ability to produce antibody formation after many exposures.

This theory would certainly explain Mulder's finding of antibody in old persons and would also account for the relatively low incidence of the disease in persons over 40 who must be presumed to have had repeated stimuli in the past from many different strains. It also makes it unnecessary to assume that there may be interepidemic or interpandemic reservoirs other than man, and it is compatible with the theory that mutants with changes in the predominant antigens are selected by the pressure of the antibody pattern of the population.

I have dealt with this subject at some length even though it must still be considered as speculative since it is obviously fundamental to our understanding of the epidemiology of influenza.

I do not propose to go into any detail regarding the laboratory findings on the Asian virus other than to say that antigenically it seems to represent the largest change yet observed in the human influenza A viruses. Other striking characteristics included the marked P–Q variation observed and the unusual sensitivity both in degree and in kind to non-specific inhibitors in different strains. Antigenically all the Asian strains seem to have been rather uniform and no change was observed in the course of the pandemic. Very recently one or two aberrant strains have been reported but this requires confirmation. These latter have not apparently behaved unusually in other ways and have not caused an unusual clinical picture.

It is notable that no reports of the isolation of previously prevalent A viruses, including the so-called Dutch 1956 strains prevalent in some areas in the winter of 1956 and spring

of 1957, have been received since the pandemic began. If 99% or more of cases were due to the new virus the older one might of course have escaped detection. However, a few B viruses have been picked up this spring. It may be that these older A strains have disappeared as did the PR8 group when the FM1 group established itself. I know of no satisfactory explanation of how this apparently complete replacement of older strains comes about.

Finally, it is by no means clear what has been happening during the first four months of 1958. Very few outbreaks have been reported and these have generally been quite local in character. Some have been in communities which escaped a heavy outbreak in the autumn of 1957. Yet in several countries there has been a considerable excess of mortality attributed to influenza and pneumonia. A good illustration of this may be found in the figures for the U.S.A. shown in Fig. 2 (U.S. Public Health Service, Communicable

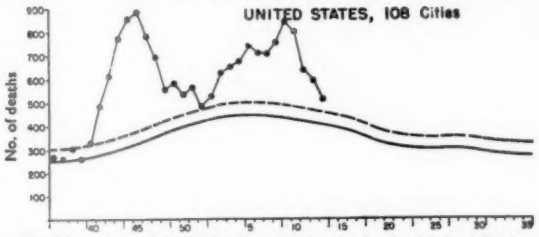



FIG. 2.—Weekly pneumonia and influenza deaths in the United States. 108 cities.

Disease Center, 1958): the weekly number of deaths in 108 cities has been almost as high as during the pandemic wave. A considerable number of individual reports received by the U.S. Communicable Disease Center Surveillance Unit indicate that this mortality was not due to recognizable epidemics of influenza. There has been some indication that deaths have been common in elderly persons with chronic chest conditions. But it must be admitted that the precise cause of this excess mortality cannot yet be defined, nor can the role, if any, of the influenza virus.

*Acknowledgments.*—I would like to express my deep appreciation to the Directors of WHO Influenza Centres, members of the WHO Expert Advisory Panel on Virus Diseases, and many other virologists, epidemiologists, and public health officials who have supplied the information contained in this paper. Thanks are due to the UNESCO *Courier* for permission to reproduce Fig. 1, and to the United States Public Health Service, Influenza Surveillance Unit, Communicable Disease Center, for permission to reproduce Fig. 2.

Thanks are particularly due to Dr. C. H. Andrewes and Dr. A. Isaacs of the World Influenza Centre for the considerable amount of data they have provided.

## REFERENCES

CHU, C.-M. (1958) *J. Hyg. Epid. Microbiol. Immunol.*, ii, 1.
——, HSIAO, C., and HO, C.-C. (1957) *Scientia, Peking*, **12,** 373.
DAVENPORT, F. M. (1958) *Publ. Hlth. Rep., Wash.*, **73,** 133.
——, and HENNESSY, A. V. (1957) *J. exp. Med.*, **106,** 835.
——, ——, and FRANCIS, T. (1953) *J. exp. Med.*, **98,** 641.
FABIYI, A. (1958) Dissertation for the Degree of Doctor of Philosophy, University of Pennsylvania.
FUKUMI, H. (1957) Personal communication.
GORDON SMITH, C. E., TURNER, L. H., and HELLIWELL, C. J. V. (1957) *Brit. med. J.*, i, 1412.
HERS, J. F. Ph., GOSLINGS, W. R. O., MASUREL, N., and MULDER, J. (1957) *Lancet*, ii, 1164.
ISAACS, A., DEPOUX, R., and FISET, P. (1954) *Bull. World Hlth. Org.*, **11,** 967.
LANGMUIR, A. D., PIZZI, M., TROTTER, W. Y., and DUNN, F. L. (1958) *Publ. Hlth. Rep., Wash.*, **73,** 114.
LIM, K. A., SMITH, A., HALE, J. H., and GLASS, J. (1957) *Lancet*, ii, 791.
MEYER, H. M., HILLEMAN, M. R., MIESSE, M. L., CRAWFORD, I. P., and BANKHEAD, A. S. (1957) *Proc. Soc. exp. Biol., N.Y.*, **95,** 609.
MULDER, J. (1957) *Lancet*, ii, 334.
PATEL, T. B., and RAO, V. N. (1957) *Ind. J. Child Hlth.*, **6,** 643.
SHOPE, R. E. (1958) *Publ. Hlth. Rep., Wash.*, **73,** 165.
SMORODINTSEV, A. A. (1958) Personal communication.
WANG, F.-F., and LIANG, Y.-K. (1957) Proc. Third International Meeting of Biological Standardization. Opatija; p. 89.
WAYBACK, M., and REYES, A. G. (1957) *Publ. Hlth. Rep., Wash.*, **72,** 855.
U.S. Public Health Service, Communicable Disease Center (1958) Influenza Surveillance Report, No. 39. Atlanta.
ZHDANOV, V. M., and RITOVA, V. V. (1959) *Bull. World Hlth. Org.*, in press.

**Dr. J. C. McDonald** (Epidemiological Research Laboratory, Central Public Health Laboratory, Colindale):

*Asian Influenza in Great Britain* 1957–58

This paper is based on reports from public health and other laboratories of positive tests for influenza virus infection, mortality and sickness claim statistics published in the Weekly Returns of the Registrar-General, and on the results of two special surveys—one in a general practice in Kent, and the other a serological study of some 600 adult volunteers in the London area.

During the past winter more than 5,000 laboratory diagnoses of influenza A were reported. This included the isolation of almost 1,000 strains of virus, most of which were typed and all of which were of the Asian variety. Most of these positive tests were obtained during the autumn epidemic, but the figures for December 1957 and January and February 1958, though less impressive, were of the same order as for the corresponding periods of 1952–53 and 1955–56 when influenza A was epidemic. Some indices of the prevalence of influenza during the past winter are presented in Fig. 1 which shows that during the autumn of 1957 there was a considerable increase in claims for sickness benefit and in mortality from all causes, roughly coinciding with laboratory evidence of influenza A. The graph is based upon the weekly excess number of deaths and claims in 1957–58 over 1953–54, a winter when laboratory evidence of virus influenza was almost completely absent (Public Health Laboratory Service, 1957). Of particular interest is the second and even greater rise in excess mortality during December and early January, not obviously accompanied by any increase in excess morbidity in the insured population, or in positive laboratory findings. The part that Asian influenza may have played in this second wave of mortality is the main question examined in this paper.

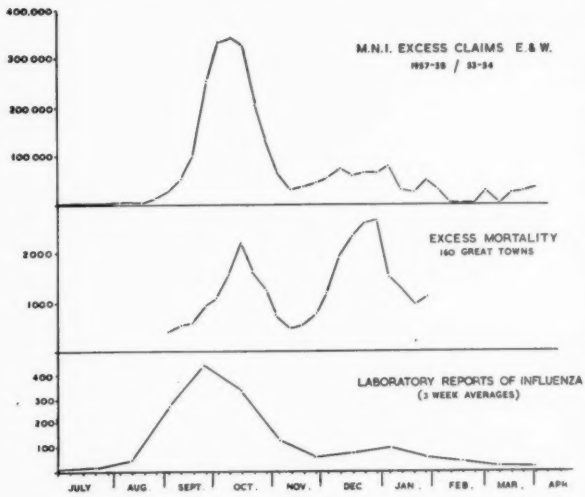



FIG. 1.

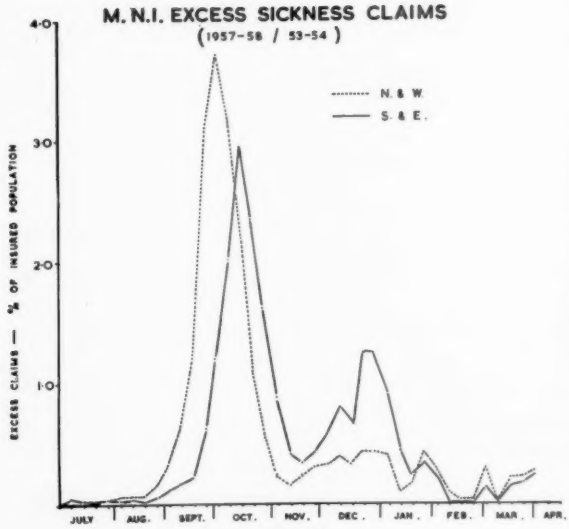



FIG. 2.

*Regional differences in morbidity and mortality.*—The general impression that the epidemic began and was more prevalent in the North

of England is borne out in Fig. 2. This shows the weekly excess claims on the Ministry of National Insurance in regions North and West of a line drawn from the Severn to the Wash, compared with regions South and East of that line. Though there was little or no evidence of a second wave in the North and West there was a definite rise in the South and East at the turn of the year. The inverse relationship between experience up to and after November is brought out more clearly when the regions are studied individually (Table I). The figures in Table I are excess claim rates per thousand of the insured

TABLE I.—REGIONAL DIFFERENCES IN RATES FOR EXCESS* SICKNESS CLAIMS ON THE MINISTRY OF NATIONAL INSURANCE

| Region | Aug. 28–Nov. 12 | Nov. 13–Feb. 11 | Feb. 12–April 1 | Total |
|---|---|---|---|---|
| Northern | 125 | 89 | 204 | 120 |
| E. and W. Ridings | 110 | 82 | 110 | 103 |
| North West | 130 | 74 | 142 | 118 |
| North Midlands | 93 | 103 | 73 | 95 |
| Midlands | 88 | 71 | 73 | 83 |
| Eastern | 94 | 145 | 92 | 106 |
| London and S.E. | 81 | 133 | 72 | 93 |
| South | 90 | 130 | 86 | 99 |
| South West | 96 | 101 | 80 | 96 |
| Wales | 114 | 89 | 137 | 109 |
| England and Wales | 100 | 100 | 100 | 100 |

*1957–58 compared with 1953–54

population in each region expressed as a percentage of the rate for the whole of England and Wales. With the exception of the Midlands, all regions with a figure of more than 100 up to November 12 had one of less than 100 during the period November 13 to February 11, and vice versa. The alternation continues during the third period from February 3 to April 1.

The Weekly Returns of the Registrar-General during the period concerned provide mortality figures for the 160 Great Towns but not for the whole population. It is therefore rather more difficult to compare mortality rates on a regional basis, but dividing the country again into two, the excess mortality rate in the North and West was higher than in the South and East during the autumn epidemic but lower during the mid-winter period (Table II). The excess mortality rates in the North and West were similar in both periods,

TABLE II.—EXCESS* MORTALITY FROM ALL CAUSES—160 GREAT TOWNS

| | Death rate per thousand population | | |
|---|---|---|---|
| | Aug. 25–Nov. 9 | Nov. 10–Jan. 25 | Total |
| North and West | 0·58 | 0·63 | 1·21 |
| South and East | 0·43 | 0·81 | 1·24 |
| England and Wales | 0·49 | 0·73 | 1·22 |

*1957–58 compared with 1953–54

whereas the rate was twice as high during the second period in the South and East. The excess mortality rates for the two periods combined were the same in both parts of the country.

*Age attack rates.*—Evidence was found in a study of Asian influenza in a Kent general practice (Woodall *et al.*, 1958) that the autumn epidemic in that particular practice was almost confined to school-age children and their family contacts. Families without school-age children were hit more lightly. As older people tend to live in families without children, this, rather than any differences in susceptibility, may have been the cause of the age gradient in attack rates. Age-specific secondary attack rates, attack rates in husbands and wives, and the order of becoming ill in family outbreaks in the Kent investigation all tended to support this conclusion. After the autumn epidemic, however, whereas a high proportion of younger people, particularly school children, had been infected and presumably acquired some immunity, the great majority of older people were probably still susceptible. Asian virus infection, smouldering on during the winter months, might therefore have been expected to affect mainly populations and parts of the country that had been spared during the autumn epidemic. Attack rates by age from clinical influenza from December to the end of February in the Kent practice, and in the serological study of volunteers in

the London area, bore this out. Whereas most younger persons who had influenza had it during the earlier period, at least as many persons of 60 years or more were ill after the epidemic as during it.

*Case-fatality rates.*—In recent years the case-fatality rate from influenza has been low and almost all the mortality from this disease has been in old people. Asian influenza was no exception; during the autumn wave 93% of the excess deaths in London administrative county during the autumn epidemic were in persons over 44 years of age and 63% were in those over 64. During December and January these proportions rose to 97% and 75% (Table III). Mortality figures by age for the whole country are not yet available.

TABLE III.—AGE DISTRIBUTION OF EXCESS* DEATHS—LONDON ADMINISTRATIVE COUNTY

| Age (years) | Aug. 30–Nov. 28 | | Nov. 29–Jan. 23 | |
|---|---|---|---|---|
| 0–44 | 122 | (6%) | 70 | (3%) |
| 45–64 | 571 | (30%) | 593 | (22%) |
| 65+ | 1,186 | (63%) | 2,018 | (75%) |
| Total | 1,879 | | 2,681 | |

*1957–58 compared with 1953–54.

By applying the age-specific morbidity rates from the Kent practice, and the excess mortality rates for London to the population of England and Wales, it is possible to obtain a rough estimate of case-fatality rates by age during the autumn epidemic (Table IV).

TABLE IV.—MORBIDITY AND MORTALITY ESTIMATES FOR ENGLAND AND WALES (Sept.–Nov., 1957)

| Age (years) | Influenza | Deaths | Case-fatality rate (per 1,000) |
|---|---|---|---|
| 0–44 | 10,020,000 | 990 | 0·1 |
| 45–64 | 2,010,000 | 4,950 | 2·5 |
| 65+ | 511,000 | 10,560 | 20·0 |
| Total | 12,541,000 | 16,500 | 1·3 |

These figures may be far from accurate but it seems clear that the rates rose steeply with advancing age. For this reason influenza morbidity in children or the insured population may not be related closely to mortality trends. Infection rates for persons over 64 would be a better index but these figures are difficult to obtain. Even with the greater laboratory facilities now available, only about 1 in 2,000 cases of Asian influenza in the autumn epidemic was confirmed by laboratory test; the proportion among old people was probably far lower.

*Summary and conclusions.*—Available evidence suggests that the autumn epidemic of Asian influenza was mainly in school children and their contacts. The age distribution of illness was probably related to opportunity for infection rather than to variation in susceptibility. After the autumn epidemic laboratory evidence of Asian influenza virus infection continued for several months at a high rate, though in comparison with October figures it was less impressive. Both sickness claims and mortality statistics suggest that those parts of the country that suffered most during the autumn suffered least during December and January and vice versa. The findings from two field surveys showed that clinical influenza attack rates in younger people were low during December and January, but that the rates for old people, though also low, were just as high as they had been during the autumn. As mortality from influenza depends almost entirely on the prevalence of infection in old people it seems possible that the second wave of excess mortality in December and January was also mainly due to the Asian virus. This hypothesis would require that case-fatality rates from influenza were somewhat higher during mid-winter than in the autumn, but this does not seem improbable.

## REFERENCES

Public Health Laboratory Service (1957) *Brit. med. J.*, ii, 8.

WOODALL, J., ROWSON, K. E. K., and MCDONALD, J. C. (1958) *Brit. med. J.*, in press.

# Section of Pædiatrics

President—A. Doyne Bell, M.A., D.M., F.R.C.P.

[*June* 28, 1958]

Meeting held at Bristol

## The Treatment of Phenylketonuria

By F. S. W. Brimblecombe, M.D., and Margaret E. R. Stoneman, M.B.

A film record was shown which demonstrated the varying effects of restriction of dietary phenylalanine on three phenylketonuric children.

*Case I.*—A male child whose pre-treatment development quotient (Griffith scale) had already fallen to 29 at the age of 9 months, suffered further deterioration during six months' treatment (development quotient 22 at the age of 15 months). The deterioration continued although the plasma phenylalanine level was reduced to normal, and for a short period to subnormal levels.

*Case II.*—A female child (sister of Case I) was less severely affected (pre-treatment development quotient 41 aged 2 years and 3 months). She improved during one year of dietary treatment (development quotient 55 aged 3 years and 3 months).

*Case III.*—This male infant was treated from the age of 17 weeks. The earliest assessments of his development indicated a progressive deterioration to a development quotient level of 51 at the age of 34 weeks. Following more drastic restriction of dietary phenylalanine, there followed a steady improvement so that this child is now, at the age of 2¼ years, within the normal range of intelligence, I.Q. 91. His dietary phenylalanine has been restricted to levels which maintain the plasma phenylalanine within normal limits.

These 3 patients illustrate how the effect of treatment may vary with the severity of the case and the age at which treatment is started. It will only be possible to draw valid conclusions about the complete prevention of mental deterioration by means of dietary treatment started in very early infancy when a far greater number of such patients have been really adequately treated. Such treatment must be sufficiently drastic to reduce and maintain the plasma level of phenylalanine at or within normal limits. The elimination of phenylpyruvic acid from the urine (negative ferric chloride test) is not a sufficiently sensitive test to be reliable as the sole criterion of adequate treatment (Hsia *et al.*, 1958).

The recommendation of Woolf *et al.* (1958) that all infants should be screened at the age of 4 to 6 weeks to exclude phenylketonuria should be supported.

### REFERENCES

Hsia, D. Y. Y., Knox, W. E., Quinn, K. V., and Paine, R. S. (1958) *Pediatrics, Springfield*, **21**, 178.
Woolf, L. I., Griffith, R., Moncrieff, A. A., Coates, S., and Dillistone, F. (1958) *Arch. Dis. Childh.*, **33**, 31.

## Hyperbilirubinæmia in Premature Infants Treated by Exchange Blood Transfusion

By Beryl D. Corner, M.D., F.R.C.P.

The toxic action of pre-hepatic bilirubin in high concentration in the plasma has now been shown to be the cause of the brain damage that results in the clinical syndrome of kernicterus. Such hyperbilirubinæmia occurs in the newborn infant not only as a result of increased hæmolysis, as in hæmolytic disease of the newborn, but also commonly in immature infants, and occasionally in those born at full term, without any evidence of blood group incompatibility. Lathe and Walker (1957) have shown that bilirubin is only excreted when conjugated by liver enzyme action to glucuronides, and it is therefore suggested that failure of this normal enzyme activity is responsible for hyperbilirubinæmia in these infants.

The dramatic reduction in the incidence of kernicterus due to hæmolytic disease after the routine use of exchange blood transfusion prompted us, in August 1955, to treat severe physiological jaundice in premature infants by the same method, slight modifications having since been introduced in order to obtain maximal removal of bilirubin. 39 premature infants and 5 full-term have now been successfully treated. One adequate exchange, using 80 c.c. blood/lb. body weight, was usually satisfactory, but in 3 babies a second exchange was necessary.

The criteria for treatment have not been easy to determine and still depend to a large

extent on clinical judgment in the individual patient. Several hundred serum bilirubin determinations by Dr. Frank Lewis in the laboratories at Southmead Hospital showed that by the method used (modified Evelyn and Malloy) 25 mg.% appeared to be the critical level above which signs of kernicterus might appear. With the exception of one infant (in whom the maximum level was 24·6 mg.%), all the treated babies reached this level and in 7 the maximum was above 30 mg.%.

The age and maturity of the baby must also be considered, since an immature infant with a rapidly rising bilirubin, with the critical level reached by the fourth day, should usually be transfused without delay, as the level is likely to continue to rise up to the sixth day, by which time signs of kernicterus may appear. In the more mature infants of 36–40 weeks, the level is likely to fall after the fourth day, so that unless early symptoms of kernicterus are present the usual procedure is to repeat the bilirubin determination twelve hours later and to defer treatment if there is no change in the level or in the clinical condition. The bilirubin estimation is then repeated twelve-hourly, and exchange transfusion is only performed if there is a rise in bilirubin or minimal deterioration in the clinical condition. In this series of treated cases, most of the infants showed increasing lethargy prior to transfusion; 2 were considered to show some rigidity and 1 vomited twice, but none showed the fully developed clinical picture of kernicterus.

This paper is mainly concerned with the follow-up of 36 treated cases in premature infants (3 cases treated in the last six months are excluded as the period of follow-up is as yet too short), but during the period of this study 10 infants in whom the level of bilirubin reached 25 mg.% or more on one estimation were not transfused and these have also been followed up.

The necessity for or value of the treatment may be assessed by three methods:

(1) Review of the previous morbidity and mortality rates from kernicterus and comparison since the introduction of treatment.

(2) A close follow-up study of the treated infants.

(3) A comparison of the treated infants with matched controls.

All these methods have been attempted.

In the seven years prior to this study, 1948 to 1954 inclusive, there were approximately 70 deaths from kernicterus of prematurity out of a total of 25,279 live births in hospital, a mortality rate of approximately 2·7 per 1,000. From 2,599 premature infants born or nursed in our premature unit during the same period there were 37 known cases of cerebral palsy among the survivors; of these 10 were definitely cases of neonatal kernicterus.

Since the introduction of treatment there have been 3 deaths in which kernicterus was present at post-mortem. These babies were admitted to hospital after birth and died on the third or fourth day with either severe respiratory or cerebral symptoms which were present from birth; minimal bile staining was present in the basal ganglia. All these babies were too ill to be transfused, but one was a twin of a baby in the treated series. There have been no cases of the typical variety of athetoid cerebral palsy in surviving transfused premature infants during this period, and no deaths following transfusion.

Complete development quotients have not been performed, but a standard type of examination that can be applied by the pædiatrician in an out-patient clinic is used for all premature infants. These are first examined at the follow-up clinic at three months, then six-weekly till 6–7 months, and two-monthly till 1 year. Subsequently three-monthly examinations are made unless an abnormality is suspected when the children are seen more frequently. As the sites of cell damage in kernicterus are the basal ganglia, Ammon's horn, and the nuclei in the floor of the fourth ventricle, particularly the cochlear nucleus, the examination has concentrated on development of locomotion, hearing and speech. The tests applied have been those associated with the normal development of locomotion, i.e. age of rolling from supine to prone, sitting unsupported, crawling and walking. Simple tests of hearing are carried out at each examination, particular emphasis being placed on the child's reactions to human speech and other familiar sounds. The development of speech from the stage of cooing and babbling to the achievement of sentences is noted. As the survey has only continued for two years and nine months the children are still too young for accurate audiometry and although it is possible to detect partial deafness at this early age, some degree of high frequency deafness cannot be definitely excluded until speech has fully developed or accurate audiometry can be performed.

## Results

In a total of 1,214 premature infants passing through the 2 maternity units from August 1955 to December 31, 1957, 36 premature infants have been treated, an incidence of 3%, which compares with the maximum yearly incidence of kernicterus in premature babies of 4·1% found by Crosse *et al.* (1955). All these infants have been followed up for longer than six months. Table I shows their present ages. There was one transfused infant in each of

TABLE I.—36 INFANTS TREATED BY REPLACEMENT TRANSFUSION

| Present age | Males | Females |
|---|---|---|
| 6–12 months .. .. | 4 | 6 |
| 12–24 „ .. .. | 9 | 2 |
| 24–36 „ .. .. | 6 | 8 |
| Died at 2 months .. | 1 | — |
| Total .. .. | 20 | 16 |

TABLE II.—BIRTH WEIGHT OF TREATED BABIES

| No. of babies | 3 lb. 4 oz. and under | 3 lb. 4 oz. –4 lb. 6 oz. | 4 lb. 6 oz. –4 lb. 15 oz. | 5 lb.– 5 lb. 8 oz. |
|---|---|---|---|---|
| 36 | 3 | 16 | 12 | 5 |

Maturity of Treated Babies

| Less than 32 weeks | 32–35 weeks | 36–40 weeks |
|---|---|---|
| 7 | 20 | 9 |

TABLE III.—FOLLOW-UP OF TREATED BABIES

*Walking Progress*

| Total No. over 1 year | 12–18 months not walking | Walking before 18 months | Walked at 18–24 months |
|---|---|---|---|
| 26 | 6 | 14 | 6 |

*Speech Progress*

| Single words before 1 year | Single words at 12–18 months | No speech at 18 months |
|---|---|---|
| 14 | 11 | 1 |

3 pairs of twins; in one pair, the other baby died at 3 days with kernicterus and was considered too ill to treat. In the other 2 pairs, the untreated babies did not develop significant hyperbilirubinæmia. One infant had an older sibling, a premature infant, who had survived severe hyperbilirubinæmia and was left with residual mild spastic diplegia. None of these infants had any evidence of blood-group incompatibility. The distribution of the treated babies by birth weight and maturity groups is shown in Table II. Table III shows subsequent developmental progress. The general physical condition of all the children is satisfactory except for one child from a rather poor home who is moderately underweight and has had recurrent respiratory infections. One child appears backward with speech but she hears and has good comprehension of language and obeys spoken commands; she is the child of a very over-anxious mother, a sick children's nurse, and her lack of speech appears to be due to negativism. One child appears to be backward in locomotion and only sits unsupported at 14 months but there is no evidence of spasticity and he is still too young to define him as outside the limit of normal in view of his immaturity at birth (31 weeks). All those children who walk do so normally for their age, and all appear to use their hands normally, and are feeding themselves with spoon and cup before 2 years. One child who was well and seemed normal on discharge from the premature unit died from an acute respiratory infection two months later. One child has not been seen as she failed to attend for follow-up since 3 months old; a report from a relative states that she is a very normal child now aged 2½ years, who runs about and talks.

Those children who have reached the age of 2 years have been compared with matched controls. The controls are premature babies who had maximum serum bilirubin less than 15 mg.% and have attended the follow-up clinics regularly and been examined in the same way. They have been matched for sex, birth weight, approximate maturity, singletons have been matched with singletons, and twins with twins. All have been free from serious disease or malformation. There do not appear to be any differences between the treated babies and the comparable controls.

An attempt has also been made to follow up the 10 babies who were not transfused. One of these has left the district and cannot be traced. One child is quite severely deaf and one has severe athetoid type of cerebral palsy and deafness. The other 7 appear to be normal healthy children.

*Conclusion.*—Replacement blood transfusion appears to be a satisfactory treatment for hyperbilirubinæmia of prematurity and the prevention of death and clinical signs of kernicterus in the neonatal period. A follow-up study shows that no cerebral palsy or gross deafness has followed in treated cases. All infants who are old enough to assess appear to be developing speech and locomotion normally, but none is yet old enough to exclude the presence of slight high frequency deafness. Criteria for the treatment are

difficult to determine but stress should be placed on clinical judgment of the individual case as undoubtedly some infants with hyperbilirubinæmia recover undamaged. Careful observation of the clinical condition and repetition of bilirubin estimation are essential in doubtful cases but even so it is possible that too many cases have been transfused.

REFERENCES

CROSSE, V. M., MEYER, T. C., and GERRARD, J. W. (1955) *Arch. Dis. Childh.*, **30**, 501.
LATHE, G. H., and WALKER, M. (1957) *Biochem. J.*, **67**, 9P.

## Heart Failure in Infants

By K. SIMPSON, M.D.

50 cases of heart failure in infants, admitted to hospital under Dr. John Apley, were reviewed to determine early signs of failure and to assess the incidence of respiratory infection.

The reason for referral was noted in 40 cases. Although 26 of these were in failure when they were first seen, a diagnosis of heart failure was made in only one case before admission. In two-thirds of the cases heart disease had not previously been suspected, diagnoses implying respiratory disease or feeding difficulty being made.

*Final diagnoses.*—In 10 infants (20%) no congenital cardiovascular anomaly was detected: 6 infants developed heart failure with acute pulmonary infection; in 4 infants failure was associated with a cardiac arrhythmia.

In 40 infants heart failure occurred with congenital heart disease. 19 of these infants had lesions for which operation offers, or may soon offer, a reasonable prospect of improvement or cure (ventricular septal defect, patent ductus arteriosus, pulmonary stenosis, coarctation of aorta, tetralogy of Fallot); 14 (73%) recovered from heart failure.

*Clinical features.*—Enlargement of liver (liver edge at least 3 fingerbreadths below the right costal margin, or liver diminishing in size after treatment): present in 40 infants. Tenderness of the liver was definitely present in a few infants.

Respiratory disturbance (respiratory rate at rest at least 60 per minute, and/or obvious difficulty in breathing on feeding or crying): present in 42 infants. Tachypnœa at rest was an early sign of cardiac failure and often preceded definite hepatomegaly by many hours, the respiratory rate rising rapidly and progressively. In early heart failure tachypnœa was not accompanied by pulmonary râles and pulmonary aeration was good. Because of the frequency of lesions producing left-to-right shunts and pulmonary engorgement (e.g. ventricular septal defect), tachypnœa developing early in heart failure was not often helpful in detecting purely left-sided heart lesions.

Cardiac enlargement (a clinical assessment based on increased transverse cardiac diameter, præcordial bulging, and thrustful substernal pulsation) was found in 27 infants. A heart which clinically seemed normal in size did not exclude the possibility of failure.

Venous distension was seen in 14 infants. Jugular venous distension was rarely visible, though in 2 infants it was noted and preceded enlargement of the liver. Distension of veins on the back of the hand or in the scalp was marked in some infants. Venous distension was frequently associated with subcutaneous œdema.

Œdema: Indisputable œdema was present in 12 infants. In 5 of these heart failure was not associated with congenital heart disease, and all recovered. The remainder, who had congenital cardiac anomalies, died.

Râles were heard in 27 infants.

When tachypnœa is associated with fever or with pulmonary râles in an infant who has congenital heart disease, the differentiation of heart failure from respiratory infection is extremely difficult, and the two frequently coexist.

Of 27 infants in whom râles were heard 6 were thought to have no evidence of infection, the râles in the latter were confined to the pulmonary bases. Basal râles were heard in one other infant in whom there was radiological evidence of bronchopneumonic infection. In the remaining 20 infants, all of whom were considered to have an infection, râles were heard throughout both lungs, or were localized to one or more lobes, and were often accompanied by rhonchi. In 15 of these infants radiological evidence of pulmonary collapse or consolidation was found.

*Other observations.*—Urinary output is difficult to assess in small sick infants. Oliguria was apparent in infants who developed œdema. Gallop rhythm was observed in 2 cases (aberrant left coronary artery and endocardial fibro-elastosis). Pulsus alternans was found once during a bout of paroxysmal tachycardia. Blood pressure recordings were not helpful in diagnosis of heart failure and may be within normal limits in cases of coarctation of aorta with heart failure.

In a number of cases in heart failure with congenital heart disease screaming after feeds and profuse sweating were noted. Heart failure should be considered when a pale, sweating infant with normal or subnormal temperature is seen.

*Incidence of respiratory infection.*—The assessment of infection was based on the history, e.g. the occurrence of coryza, the presence of pulmonary rhonchi, clinical pathological data, radiological and post-mortem evidence.

In 6 cases bronchopneumonia precipitated cardiac failure in the absence of detectable cardiovascular anomaly. All recovered after treatment. In 3 cases infection was associated with cardiac arrhythmia, 2 cases recovered.

No evidence of infection was found in 21 cases. 14 infants (66%) in this group died, the majority having severe and complicated malformations.

Of 20 cases with respiratory infection 9 died (45%). 6 of the fatal cases had cyanotic congenital heart disease, and in 4 of these the infection appeared confined to the upper respiratory tract. In the remainder pulmonary consolidation or collapse was found.

The overall mortality in this series was 48%. 15 out of 16 infants, with right-to-left shunts large enough to produce cyanosis, died, the presence of respiratory infection making little difference to the outcome. Of 24 infants with acyanotic congenital heart disease, 8 died. In this group infection probably played a bigger part in precipitating failure, and may improve the prognosis of heart failure if the infection can be successfully treated with antibiotics.

## A Common Denominator in the Recurrent Pains of Childhood

By John Apley, M.D.

The observations which follow represent the salient points from studies on groups of children, seen at school or at hospital, with pains recurring predominantly in the limbs, abdomen or head. In contrast to adults, in children these are the only common sites of pains which recur over a considerable time. The studies were carried out over a period of several years, independently of each other, and with different collaborators. They are reported fully elsewhere: it is only recently that I have collated the results and realized how closely similar they are.

*Limb Pains* (Naish and Apley, 1951)

Frequency: 4% among unselected school children.

Incidence of major organic disease: 3% to 4% of investigated cases.

Significant emotional disturbances: in half to three-quarters (cf. less than one-fifth in controls).

Relevant family histories: three-quarters had "rheumatism" of some sort (cf. one-tenth in controls) with a suspected but uninvestigated relationship with emotional disorders.

*Abdominal Pains*

Frequency: 11% among unselected school children (Apley and Naish, 1958).

Incidence of major organic disease: about 6% of investigated cases (Apley, 1959).

Significant emotional disturbances: in two-thirds (cf. one-fifth in controls), many with characteristic personality traits.

Relevant family histories: similar pains in half, and an incidence of "nervous" disorders several times higher than in controls.

*Head Pains*

Though recurrent headaches are certainly common I have no figures for frequency among unselected school children.

Incidence of major organic disease: less than 5% of investigated cases.

Significant emotional disturbances: in three-quarters.

Relevant family histories: similar pains in three-quarters, and "nervous" disorders in a very considerable proportion.

*Links Between the Three Groups*

The above data bring out some interesting resemblances between the three groups of children. The large majority have no major physical disease to which the main presenting symptom can be attributed; emotional disturbances are very common, and their manifestations strikingly similar; the families are prone to similar pains and to "nervous" disorders. The "choice of symptoms" in child and in parents is a territory which is relatively unexplored.

Against this background one might suspect a common ætiology in all three groups. This possibility is supported by some features of the pains themselves. Taking the histories in careful detail I find that, though the pains nearly always predominate in one site, in more

than a third of cases pains occur also in one or both of the other sites, either at the same or at different times. There is also considerable interchangeability between the pains. Thus, pains in one site are sometimes substituted for pains in another, often without apparent cause; a similar substitution was of special interest in a "blind trial" in which children with recurrent abdominal pains were treated with phenobarbitone to compare its efficacy with that of a placebo (Apley, 1959). Again, a change from one site to another is not uncommon as the child grows up; in a small retrospective survey of young adults who had suffered from recurrent abdominal pains in childhood, in many of the cases they had been replaced by recurrent headaches or other pains (data to be published).

*Conclusions*

There are suggestive links between the common, recurrent, non-organic pains of childhood, whether they occur in the limbs, abdomen or head (the only common sites in this age-group). Interesting similarities are observed, not only between the children who suffer from these pains but also between their families.

It is suggested that these pains be grouped together, as expressions of a reaction pattern which is usually associated with emotional disturbance and is often part of a familial pattern of disorder.

REFERENCES

APLEY, J. (1959) In the press.
——, and NAISH, N. (1958) *Arch. Dis. Childh.*, **33**, 165.
NAISH, J. M., and APLEY, J. (1951) *Arch. Dis. Childh.*, **26**, 134.

## The Vascular Factor in Birth Injury

By A. V. NEALE, M.D., and H. URICH, M.D.

**Professor A. V. Neale:** It is now fully appreciated that a concatenation of circumstances may be more injurious to the fœtus or the newborn than any single or separate incident. Dangers lie in various ways in anoxia-asphyxia, extravasation of blood, venous and capillary congestion, arterial failure, sudden intracranial shifts, reactionary meningo-cerebral œdema. Consequences lie in the direct cerebrospinal effects or in consequential physiological failure at or soon after birth.

There is probably a unique system of defence at birth in connexion with the circulatory dynamics. The adjustments in the circulation are complex. The cerebral blood flow must be maintained against several possible disturbing influences. The change-over from the fœtal to the open pulmonary circulation is significant in equalizing the pressures in the right and left heart. The output of the left ventricle increases to feed the new systemic arterial circuit and normally there is still circulatory priority to the brain.

The pressor amine noradrenaline is present in relatively large amounts in the para-aortic bodies and the adrenal medulla (in fact it reaches a maximum at full-term) falling rapidly in the week after birth. It is possible that this provides a method of defence against "shock" at birth. The action of noradrenaline is to raise the systemic blood pressure and maintain an improved arterial flow to the brain and heart. It does not, however, raise the blood sugar. The cerebral function is satisfactory, provided the oxygenated arterialized blood flow is adequate. A fall in the blood sugar at this stage is common but not serious. But hypoxia and hypoglycæmia are a serious combination in the brain. Mobilization of liver glycogen to glucose is relatively slow in the newborn—adrenaline is practically absent and the glucocorticoid responses meagre. Hence the imperative need for an effective arterial distribution in all parts of the brain.

**Dr. H. Urich:** The lesions encountered in the brains of children who have survived severe cerebral birth injury fall into certain recurrent patterns. In the cerebral cortex the lesions take the form of focal scars of variable extent and distribution, but with predominance in the parieto-occipital region. The affected areas may show dense sclerosis or softening with superficial cavitation. These lesions represent healed scars of old infarcts, either arterial or venous.

In the white matter one of two patterns can be seen. One consists of shrinkage of the central white matter, with an area of demyelination or softening adjacent to the lateral angle of the ventricle, sometimes with radial scars extending from the ventricles into the white cores of the gyri. This is a typically venous pattern caused by stasis in the territory drained by the great vein of Galen. The other pattern consists of extensive cavitation of the white matter and is known as cystic encephalomalacia or polyporencephaly. The pathogenesis of this lesion is still obscure.

In the basal ganglia the most characteristic lesion is *état marbré* of the striatum which consists of a dense network of myelinated fibres in an area of fibrous gliosis. It is

commonly associated with lesions in the pallidum, thalamus, Ammon's horn and amygdaloid nucleus. *État marbré* is considered to be a non-specific response of the infantile striatum to partial damage which may be due to various factors, such as anoxia, venous stasis and perhaps also interference with the arterial circulation.

The importance of the venous factor in cerebral birth injury was stressed by Schwartz (1924) and little can be added to his monumental work though some of his generalizations are no longer acceptable. On the other hand the arterial factor has suffered from considerable neglect due largely to the ignorance which prevailed until recently of the many possible variations in the severity and distribution of arterial lesions. It is now known that the classical pattern of destruction of the entire territory supplied by a single artery is comparatively rare and occurs only if occlusion of the artery is accompanied by failure in anastomotic circulation. An efficient anastomotic circulation will modify the appearance of the lesion considerably and reduce its extent. A different pattern will be produced by simultaneous reduction in blood flow in two arteries supplying adjacent territories: here the damage will be most severe in the boundary zone between the two arterial territories.

All these patterns known from observations on occlusive arterial disease in later life can be found in cases of birth injury. Total destruction of an entire arterial territory is rare and is usually seen in the part supplied by the middle cerebral artery. Lesions corresponding to the distribution of individual branches or their parts are more commonly found, particularly in the territory of the posterior cerebral artery. Here the calcarine artery which supplies the visual cortex is most commonly affected, but other branches may also be involved singly or in combination. Lesions of the arterial boundary zones may be seen either in the frontal lobes between the territories of the anterior and middle cerebral arteries, or the parieto-occipital regions between the middle and posterior arteries.

In the pathogenesis of these lesions both general and local factors play a part. It is known that generalized insufficiency of the arterial circulation such as occurs in shock with profound fall in the arterial blood pressure may give rise to focal lesions in the brain which are often localized in the arterial boundary zones, but may also affect other terminal arterial territories. Local factors include mechanical compression, stretching and kinking of individual arteries during displacement of the brain. The points of compression and the conditions under which it may occur are now well known from Lindenberg's (1955) work on the effects of raised intracranial pressure. In birth injury both the anatomy of the dural folds and the mechanics of head presentation favour a distribution of lesions in the posterior half of the brain. Arterial compression is greatly facilitated by a simultaneous fall in blood pressure. Lesions which can be ascribed to general circulatory and to local mechanical factors are therefore commonly found side by side (Norman *et al.* 1957). To these two factors a third may be added: the respiratory factor of anoxia. This probably plays a dual role: intra-uterine asphyxia may precipitate neonatal shock, while inadequate oxygen saturation of the arterial blood may aggravate the effects of partial ischæmia. Finally the factor of prematurity is worthy of mention since a high proportion of these lesions are observed in premature infants. Whether that is due to the fact that the arteries are thinner and more easily compressible or to a more labile blood pressure remains an open question. Very little is known about neonatal blood pressure, and further studies in normal, premature and birth injured infants would be desirable.

These conclusions are based upon work carried out with Dr. R. M. Norman at Frenchay Hospital and assisted by a grant from the Nuffield Foundation.

## REFERENCES

LINDENBERG, R. (1955) *J. Neuropath.*, **14**, 223.
NORMAN, R. M., URICH, H., and MCMENEMEY, W. H. (1957) *Brain*, **80**, 49.
SCHWARTZ, P. (1924) *Z. ges. Neurol. Psychiat.*, **90**, 263.

**Peritoneal Drainage in the Treatment of Hydrocephalus.**—G. L. ALEXANDER, B.Sc., M.D., F.R.C.S., D. G. PHILLIPS, M.B., F.R.C.S., D.L.O., and A. HULME, M.B., F.R.C.S.

Many methods have been tried for the relief of blockage to the free circulation and absorption of C.S.F., when there is obstruction in the subarachnoid pathways. The problem is a particularly difficult one, and no method so far devised gives consistently satisfactory results.

The method of passing a tube, either from a lateral ventricle or the lumbar sac, into the peritoneal cavity has the merit of simplicity and the results are, in general, no more disappointing than those of other methods which have been tried.

A review is presented of 28 cases (22 ventriculo-peritoneal and 6 theco-peritoneal) of drainage operations, carried out in Bristol (Table I). The majority of these were for infantile hydrocephalus associated with spina bifida.

The record is by no means satisfactory, though encouraging results have been obtained in, perhaps, one-third of the cases. This is in line with experience in other centres.

It is, perhaps, worthy of note that the rate for spontaneous remission of hydrocephalus in these cases is also about 30%.

TABLE I.—ANALYSIS OF 28 PERITONEAL DRAINAGE OPERATIONS FOR C.S.F. BLOCKAGE
(22 ventriculo-peritoneal, 6 lumbar theco-peritoneal)
17 male, 11 female

| | |
|---|---|
| *Age:* Less than 6 months | 14 |
| 6 to 12 months | 10 |
| Over 1 year | 4 |
| *Associated disease:* | |
| Spina bifida | 15 |
| Infantile hydrocephalus unassociated with spina bifida | 8 |
| Post meningitic hydrocephalus | 3 |
| Birth injury | 1 |
| Posterior fossa tumour | 1 |
| *Results* | |
| Good, i.e. believed to be functioning satisfactorily at present (Longest period two years and two months) | 10 |
| Probable spontaneous remission | 2 |
| Dubious, i.e. drainage doubtful or intermittent | 2 |
| Living but known to be failures (blockage, infection, tube removal, &c.) | 5 |
| Dead | 7 |
| No recent follow-up available | 2 |

**Some Observations on Avian Osteopetrosis.**—J. R. HOLMES, M.V.Sc., Ph.D., M.R.C.V.S.

This condition in the fowl was demonstrated owing to the resemblance of some of the lesions radiologically to those of infantile cortical hyperostosis (Caffey's syndrome) (Figs. 1, 2 and 3).



FIG. 1.—A.P. of fowl tibia showing early changes in the midshaft of the bone.



FIG. 2.—A.P. of fowl metatarsal showing extensive periosteal new bone and also cortical and endosteal changes.



FIG. 3.—Radiograph of a case of human Caffey's disease for comparison.

The disease develops in the skeleton of the growing bird, being characterized initially by a periosteal proliferation of the diaphyses of the long bones. The lesions are generally bilaterally symmetrical. The condition usually becomes clinically evident at about 3 months of age, when visible thickening of the metatarsi occurs and this may become so extensive that the legs assume a boot-like appearance.

The disease can be transmitted experimentally using whole blood, bone marrow and Seitz EK filtered plasma from affected birds inoculated intraperitoneally into day old chicks. It can also be transmitted by intra-amnion inoculation, and the egg is probably an important mode of natural spread.

Radiologically the initial periosteal reaction in the long bone diaphyses is later accompanied by similar reaction in the endosteum and increasing density of the long bone shafts. The long bones therefore become wider and denser than normal (Fig. 2).

Histologically there is initial subperiosteal hyperæmia followed by the formation of new subperiosteal bone.

This disease appears to be of viral origin. In natural and experimentally produced cases recovery has not been observed.

**Regional Ileitis in Children.**—C. H. TALBOT, F.R.C.S.

Two cases of "acute" regional ileitis have been seen personally in recent months in children aged 6 and 8 years respectively. The clinical diagnosis in each case was acute appendicitis and the true diagnosis made at laparotomy.

*Case I.*—A boy aged 6 years was admitted to the Children's Hospital, Bristol, on 21.2.58 as an emergency. One month before admission he had central abdominal pain for three days accompanied on the first day by vomiting and on the third day by several loose stools. Thereafter he was symptom free until forty-eight hours before admission when he again complained of central abdominal pain. This became more severe six hours before admission, he vomited three times and he passed three loose stools.

He was a normally developed boy of average weight. His temperature was 99° F. There was acute tenderness in the lower abdomen with definite rigidity in the right iliac fossa and there was peritoneal tenderness on rectal examination.

A clinical diagnosis of acute appendicitis led to his abdomen being explored through a McBurney incision. The peritoneal cavity contained a moderate amount of free fluid. An inflammatory mass found lying over the pelvic brim was delivered into the wound. It was found to consist of loops of terminal ileum adherent to each other with the appendix buried between them. The appendix proved to be normal when it had been dissected free from the mass. The diseased loops of bowel were red and thickened and there were patches of yellow exudate on their serosal surface. They were firmly adherent to each other. The mesentery was thickened and contained enlarged glands. The diseased loops were resected (24 cm. of bowel) and as the terminal 3 inches (7·5 cm.) of ileum appeared normal an end-to-end ileo-ileal anastomosis performed. The appendix was removed.

The post-operative course was smooth and he was well when seen three months later.

The gross specimen showed marked submucous thickening typical of regional ileitis and a perforating ulcer was found near the distal end of the segment removed. The histological appearance (*see* Figs. 1 and 2) is characteristic of regional ileitis.

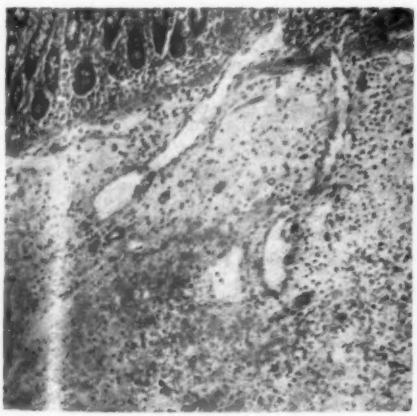


FIG. 1.—Ileum showing submucosal œdema and dilated lymphatics.

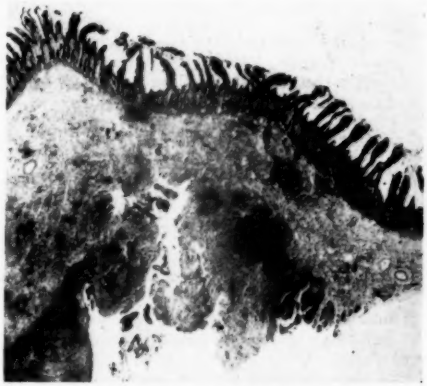


FIG. 2.—Necrosis and inflammatory change in ileum at site of fistula.

*Case II.*—A boy aged 8 who had previously been healthy was admitted to Bristol Royal Infirmary as an emergency on 27.2.58 with a thirty-six-hour history of central abdominal colicky pain and repeated vomiting.

He was a rather small thin boy with a temperature of 99° F. His tongue was furred and his breath fetid. There was acute tenderness with guarding in the right side of the abdomen rather above McBurney's point.

Following a diagnosis of acute appendicitis the abdomen was explored through a McBurney

incision. The peritoneal cavity contained a moderate amount of straw-coloured free fluid. The appendix was normal. Almost the whole ileum was thickened; much of it was bright red in colour but the colour change was present in short stretches three or four inches in length. This gave the impression of "skip" lesions often described in regional ileitis but the bowel between these red areas was thickened. The mesentery was œdematous and contained enlarged glands. The appearances were considered to be typical of a fairly extensive acute regional ileitis. The bowel was returned to the abdomen which was then closed. The appendix was not removed.

He made a rapid recovery and returned home after ten days. Three months later he was symptom free and a barium follow through was normal. There was no excess fat in the stools.

These cases are recorded largely as a reminder that regional ileitis may occur in children. In large published series (Ravdin and Johnston, 1939; Van Patter *et al.*, 1954) and in 60 cases seen at Bristol Hospitals about 5% were under 10 years of age.

It has been customary to subdivide regional ileitis into "acute" and "chronic" (Crohn, 1949). Van Patter *et al.* (1954), reviewing a large series, state that "acute" manifestations merely reflect involvement of the serous coat in the chronic disease. My experience coincides with that of Austin (1956) who regards the acute form of the disease as an entity with a favourable prognosis.

*Main clinical features.*—These may be summarized as follows:

| *Acute ileitis* | *Chronic ileitis* |
|---|---|
| Pain, colic or continuous | Colic |
| Vomiting | Diarrhœa |
| Diarrhœa | Loss of weight |
| Tenderness in right iliac fossa | Anæmia |
| Abdominal mass if not obscured by guarding or rigidity | Abdominal mass |
| Fever | Fever |
| | Blood in stool |
| | Steatorrhœa |
| | Fistula |
| | Impaired physical development |

Acute ileitis resembles acute appendicitis so closely that laparotomy is usually necessary before the diagnosis can be made. This is particularly true in children.

*Treatment.*—Since nothing is known about the ætiology opinions on the place of surgery vary. Resection as opposed to short circuit-exclusion procedures for the chronic form of the disease has in recent years been more extensively practised. It appears to show a lower morbidity without increased mortality.

*Acute regional ileitis.*—The vast majority resolve and do not progress to the chronic form (Austin, 1956). Laparotomy is usually necessary to establish the diagnosis and when this is the case appendicectomy does not appear to lead to fistula formation provided the cæcum is not obviously diseased.

*Chronic regional ileitis.*—The indications for resection (or alternatively exclusion) are: (1) Fistula formation, (2) intestinal obstruction, (3) recurrent peri-anal suppuration, and (4) failure to improve on conservative management.

Contra-indications to resection are: (1) Extensive disease involving great length of bowel, (2) no previous trial of conservative management.

*Acute exacerbation of chronic disease.*—Case I probably comes into this group. If a laparotomy is performed as a result of a wrong diagnosis and the diseased segment is short, resection is justifiable. If the disease is extensive, closure of the abdomen and a trial of conservative management is wiser. In Case I the resection should have been wider since histology shows disease extending up to the line of bowel section.

*Acknowledgments.*—I wish to thank Mr. J. A. Pocock and Mr. R. E. Horton for permission to record their cases and Dr. M. E. H. Halford for the photomicrographs and his comments on the histology.

## REFERENCES

Austin, W. E. (1956) *Canad. med. Ass. J.*, **74**, 289.

Crohn, B. B. (1949) Regional Ileitis. London.

Ravdin, I. S., and Johnston, C. G. (1939) *Amer. J. med. Sci.*, **198**, 269.

Van Patter, W. N., Bargen, J. A., Dockerty, M. B., Feldman, D. V. M., Mayo, C. W., and Waugh, J. M. (1954) *Gastroenterology*, **26**, 347.

# Section of Urology

President—LESLIE N. PYRAH, M.Sc., Ch.M., F.R.C.S.

[*April* 25, 1958, contd. from November *Proceedings*, p. 971]

MEETING AT THE GENERAL INFIRMARY, LEEDS

## Elective Prostatectomy

By Professor E. WILDBOLZ

*Berne, Switzerland*

SHORTLY after the last war I spent a couple of weeks with one of the best-known American resectionists, in the hope of improving my transurethral technique. He took me along one day to watch a resection on one of his colleagues, a surgeon of a neighbouring town, who used to refer a great many patients to him. Curious as I am, I wanted to know the symptoms, the residual urine, the result of the kidney function tests or urography and so on. The resectionist turned round rather impatiently and asked: "My dear man, how do you suppose I know? I saw the man once in my office, complaining of nocturia once or twice and a slow stream, I have not seen him since." "How can you be sure he needs a prostatectomy?" was my reply. We found the man under a general anæsthetic draped for operation. The operator stuck a cystoscope in, looked, then turned round to me: "You're right, he does not need an operation."

Could that be called elective prostatectomy?

This true story is maybe a little crude, but by no means extraordinary. If one listens to urologists in different countries to find out their indications for prostatectomy the usual answer is: It all depends. Evidently everybody is of the same opinion if the patient has an overflow incontinence or some degree of uræmia. But what about the vast majority of the patients in our offices, who complain about a moderate amount of prostatic symptoms? Is operation really the only answer to their problem? Are we not doing our best if, instead of recommending prostatectomy, we just advise them to stop drinking cocktails?

It is extraordinary how little the problem of indications for prostatectomy has moved the minds of urologists compared to the burning interest they show in any small change in the technique of prostatectomy. After all, prostatectomy is probably the most frequent operation for each of us and its indications must be clear in the mind of everyone. These indications will not be monotonously and uniformly the same with everybody

During recent years some interest has been shown in this topic. George Prather (1956), in his Presidential Address to the American Urological Association, raised the question without trying to give an answer. Gironcoli in his journal *Urologia* has accepted the challenge and made an inquiry. The answers of the fifty-two authors which have been published up to now make apparent a total lack of agreement.

Is it really impossible to come to some understanding? Are there no pathological facts, that, by reasoning, can lead to a better understanding of the problem?

I think that these pathological facts very definitely exist.

We all know that prostatic hypertrophy is a very common disease. Older statistics tell us that one man in six over the age of 40 is a prostatic, or that at autopsy one-third of all male bodies over 30 show an increase in the size of the prostate.

Aschoff thinks that in his material prostatic hypertrophy ranks as the third cause of death in males over 65. Reischauer writes that between 50 and 70 years of age neoplastic nodes in the prostate are the rule.

For precise information only autopsy statistics are of value and here again only information from those who have examined the prostates microscopically.

I should like to cite two reports for their accuracy. Kato in Japan observed in 1939 that at autopsy 9% of all men over 30 show nodules in the prostate big enough to be seen without the help of the microscope. These nodules get bigger and more frequent with advancing age, so that every third man over 60 and every second man over 70 shows a nodular prostate. Carefully examining the prostates with the microscope he finds hypertrophic nodules in 91% of all men over 70.

Howald in Basel achieved similar results in a study he made in 1948. At two hundred

consecutive autopsies performed on men he found no hypertrophy of the prostate in the first four decades of life. Over 40, characteristic nodules began to appear that were only visible with a magnifying glass and microscopically proved to be characteristic nodules of hypertrophy. With advancing age these nodules increased in number and size; after the 66th year he found them in every prostate.

These two reports lead us to a very important conclusion: hypertrophy of the prostate is not a disease, it is a physiological accident of old age and as such is not to be taken more seriously than greying or falling hair.

It is usually admitted that one-quarter to one-third of all men over 70 suffer or have suffered from symptoms due to their prostatic hypertrophy. One-third of these patients require medical help and are therefore candidates for prostatectomy.

They are candidates for prostatectomy because the first fundamental complication has arisen which changes it into a disease; the prostate interferes with micturition. Therefore, prostatectomy need never be discussed in uncomplicated cases. If we consider early prostatectomy to be necessary before any complications have arisen, I know of only two propositions that are logical. In 1937 Boeminghaus proposed to do a small transurethral resection on every man over 45, thus removing the peri-urethral submucous gland above the verumontanum, the glands in which hypertrophy originates. In 1956, Gil-Vernet repeated this proposition, modifying it to the more innocuous electrocoagulation of the same region.

If we discuss elective prostatectomy to-day, we do not talk of the group of men just mentioned; we talk about men who begin to show symptoms of disturbed micturition. Shall we without a second thought advise these patients to have their prostates removed? A charming, white-haired urologist in San Francisco who certainly cared for and looked after his patients as well as he could, on being asked by me why he wanted all his prostatics to be operated on at once, said: "Because if I didn't, I would not do the best for my patients." This opinion is shared by all those who think that a prostate giving rise to symptoms will go on doing so, the symptoms going from bad to worse, the clinical course of prostatic hypertrophy being inexorably progressive. The only logical deduction is early prostatectomy, as soon as you can lay hands on the patient. The risk of the operation will be small as the patient is young and he will enjoy more years of good health than if we postpone the operation. Boeminghaus says that medical advice must be based on the fact that, though the course of the disease may vary, it will always be downhill. But is this really a fact? I could not find a single article in the whole medical literature to sustain such an assumption. All of us remember patients who showed this steady downhill course till operation or indwelling catheter became a necessity. But the scanty articles on this subject show that they are not the rule, nor even a majority.

Compared with a wealth of literature about prostatectomy that could easily fill your library, the three articles I could find dealing with the fate of the prostatics that were not operated on look rather thin and forlorn. They are articles by Clark (1937), Barnes and Heitman (1949) and myself (Wildbolz, 1948).

Clark observed 93 patients at the Peter Bent Brigham Hospital in Boston over an average of four years. They were all prostatics who had refused prostatectomy or where prostatectomy was not advised. In 60 of them prostatectomy seemed not indicated on account of the slightness of the symptoms; in 30 prostatectomy was clearly indicated. In summary he showed that many of these patients improved and were seemingly cured after a slight amount of instrumentation. Clark intended his series to be a control for the evaluation of the effect of androgen or other hormone treatment.

Barnes and Heitman (1949) describe the course of 310 patients who were treated palliatively for one to six months in an effort to establish the prognosis of the disease in patients who did not undergo immediate prostatectomy. I am particularly interested in the group of 131 cases who were on the borderline for prostatectomy. Of these, 40% were operated on later. In a group of 83 who were advised prostatectomy but refused it at first, 77% were operated on later.

My series was undertaken in 1948 after I came home from a prolonged trip to the United States. I had gone there with an inherited, rather strict indication for prostatectomy and was worried by the very active attitude of my American colleagues. So many men cannot be wrong, I argued with myself. I sent a questionnaire to 311 of my office patients who had come to me with typical symptoms of hypertrophy of the prostate, symptoms I thought so slight as not to warrant operation. The visits lay one to ten years back. One out of three of the patients (exactly the same percentage as in Barnes' paper) had undergone prostatectomy later, one-third still had the same slight symptoms of prostatism and in one-third all the symptoms had disappeared with or without palliative therapy. One man was so thoroughly cured that he had even forgotten his troubles and thought that he had visited me on account of his rheumatism.

One fact, I think, comes out clearly from all these three papers: Hypertrophy of the prostate is not an inexorably progressive disease. It may stop its course at practically any level; it may even go into reverse and show spontaneous improvement that may be lasting.

Unfortunately we have, as far as I can see, no possibility of foreseeing this development. If we do not advise immediate operation I think we must insist upon regular visits once or twice a year for five years. If the symptoms have not progressed after that time, we may dismiss the patient definitely. I have the impression, with large prostates in younger men, that the presence of a residual urine of over 50–60 c.c. will lead sooner or later to operation and I rather tend to advise prostatectomy readily to these patients.

To sum up, uncomplicated hypertrophy of the prostate is not a disease, it is a semi-physiologic change of old age; it never gives occasion for an operation.

In a certain percentage of old men hypertrophy of the prostate disturbs micturition; this complication changes hypertrophy of the prostate into a disease that can slowly progress to be a menace to the life of the patient. This progression can stop at any level and can even regress.

Somewhere along the line of this deterioration of health, prostatectomy has its place and every urologist should get a clear vision when in his opinion the moment for prostatectomy has come. Surely the first visit to a urologist's office should not in itself be such a "deterioration of health" as to warrant prostatectomy.

My own indications for prostatectomy are as follows:

(1) Residual urine constantly over 200 c.c.

(2) Marked frequency of urination depriving the patient of sleep at night and of his enjoyment of work and play during the day.

(3) Repeated, heavy bleeding.

(4) Repeated acute retention, above all in people who travel a great deal or live far away from a doctor.

(5) Suspicion of early malignancy. Here, naturally, only a radical prostatectomy can be of any help.

But quite a few of our patients will not be happy, if they are merely told that they do not need an operation; some of them want and need relief from a certain, maybe passing deterioration. Let me take as an example a man who came to my office last week. He was a man of 55, usually very active, who used to get up once or twice a night without being much disturbed in his sleep and during the day was not a bit troubled by his prostate. This man broke his leg skiing and was confined to bed for eight weeks. During this time his prostate troubles got much worse. He has no residual urine to speak of, but his nocturia has risen to five to six times, his stream is weak and he gets nervous and is ready to accept a prostatectomy, if no other treatment can be offered. I was pretty sure that all his troubles would go away as soon as he could resume his activities in full. Conservative treatment was clearly indicated; we probably all give the same advice on hygiene and diet, without too much conviction; we may add instrumentation or prostatic massage, again without too much conviction.

I would recommend that, in a case like this, treatment by œstrogens should be tried. If my information is correct, œstrogenic treatment of benign hypertrophy of the prostate has not met with great favour in Great Britain. I have been using it now for over thirteen years and am as content with its results as on the first day. A good result may be expected in two-thirds of the cases, a lowering of residual urine in every second patient and, strangely, the occasional disappearance of a cystitis that has previously resisted all antibiotics. This result is achieved with a daily dose of 3–5 mg. of stilbœstrol for four to six weeks. I do not want or pretend to replace prostatectomy by hormonal treatment; I do not even think that œstrogens change the course of the disease, but given intermittently they certainly can offer a patient a great deal of relief, when prostatectomy is not indicated or is refused by the patient. Given permanently to an inoperable patient they can occasionally avoid the need for an indwelling catheter.

## REFERENCES


BARNES, R. W., and HEITMAN, C. E. (1949) *Calif. Med.*, **70**, 93.
BOEMINGHAUS, H. (1937) *Dtsch. med. Wschr.*, **63**, 1548.
CLARK, R. (1937) *Brit. J. Urol.*, **9**, 254.
GIL-VERNET, S. (1956) *Acta urol. Belg.*, **24**, 197.
GIRONCOLI, F. DE (1958) *Urologia*, **28**, 113.
HOWALD, N. (1948) *Helv. chir. Acta*, **15**, Suppt. IV.
KATO, M. (1939) *Mitt. allg. Path. Sendai*, **10**, 32.
PRATHER, G. (1956) *J. Urol.*, **76**, 131.
WILDBOLZ, E. (1948) *Helv. chir. Acta*, **15**, 251.

[*May* 22, 1958]

## VESICO-INTESTINAL FISTULA [*Abridged*]

**Mr. H. E. Lockhart-Mummery** (London):

Vesico-intestinal fistula is a condition where co-operation between urologist and bowel surgeon is of particular value, and as it is rare no one surgeon is likely to see many cases, and I am sure it will be helpful to air some of the difficulties. I propose to discuss the subject in general, with reference both to the published cases and to those that we have had at St. Mark's Hospital during the last ten years. My colleagues have kindly allowed me to review their cases, and with these and a few personal cases, both in St. Mark's and in other hospitals, the notes of 25 cases have been available for study.

When one explores the literature on vesico-intestinal fistula, all roads lead back to Harrison Cripps (1888) who reviewed the whole subject, collected the clinical details of many published cases, and added 3 of his own. Later publications gradually built up the pattern of essential facts as we know them today. During the seventy years since Cripps first published his paper, there has been some alteration in the causes of the condition, there has been some improvement in diagnosis and considerable improvement in treatment, but one cannot read his monograph without admiration for the clinical observations and wisdom contained therein.

All writers on vesico-intestinal fistula seem to agree on the different incidence in the two sexes, the condition in males being three to five times commoner than it is in females. This is, of course, partly accounted for on purely anatomical grounds, but it is not the whole explanation as the incidence of diverticulitis and its complications is known to be greater in men. As to the ætiology of the condition, the causes fall conveniently under the four classic headings of congenital, traumatic, inflammatory and neoplastic. Various figures of the different percentages in each group are available in the literature, but it is of little use to discuss collected figures. For one thing, the practice of different hospitals varies according to the type of case they admit, and for another, there have been changes in the ætiology of this condition over the years. In many early reports, the nature of a lump in the pelvis was uncertain, and often assumed to be malignant without much evidence. In many of these early reports, also, tuberculosis was mentioned as a common cause, whereas now it is very rare, and regional ileitis as a cause has only been recognized since the publication of Crohn's paper twenty-six years ago (Crohn *et al.*, 1932). Nowadays, in the practice of most surgeons, the majority of cases of vesico-intestinal fistula are due to diverticulitis, with carcinoma of the bowel as the second most common cause, and the other causes a poor third.

This generalization may not apply for surgeons whose main practice is in pædiatrics, as the congenital type of vesico-intestinal fistula is nearly always associated with an imperforate anus and forms part of the management of that problem. These cases form a special group of which I have little experience.

There are two main types of traumatic fistula, the one following injuries from foreign bodies, including shell fragments and bullets, &c., and also injuries following impalement; and the other following surgical operations, nearly always prostatectomy or bladder neck resection. The latter group are particularly difficult.

The inflammatory group is the largest and, in this, diverticulitis of the sigmoid is by far the most common lesion. The next most common seems to be Crohn's disease of the terminal ileum, but it has been estimated that only about 1 case in 50 of the latter forms a vesico-intestinal fistula (Williams, 1954). Then there are several rarer inflammatory causes, such as appendicitis, inflammation around a swallowed foreign body, such as a fishbone impacted in the sigmoid colon, inflammation in a Meckel's diverticulum, and even prostatitis with abscess formation. Other more bizarre causes are occasionally recorded in the literature.

TABLE I.—CASES OF CARCINOMA AT ST. MARK'S HOSPITAL: 1928–1952 INCLUSIVE

| | Rectum and rectosigmoid | | | Sigmoid colon | | |
|---|---|---|---|---|---|---|
| | No. | Total | % | No. | Total | % |
| *Adherent to Bladder* | | | | | | |
| Males .. .. .. | 129 | 2,323 | 5·6 | 14 | 183 | 7·65 |
| Females .. .. | 9 | 1,143 | 0·8 | 5 | 131 | 3·8 |
| Total .. .. | 138 | 3,466 | 4·0 | 19 | 314 | 6·05 |
| *Fistula into Bladder* | | | | | | |
| Males .. .. .. | 15 | 2,323 | 0·6 | 6 | 183 | 3·3 |
| Females .. .. | 1 | 1,143 | 0·1 | 1 | 131 | 0·76 |
| Total .. .. | 16 | 3,466 | 0·46 | 7 | 314 | 2·2 |

Of the neoplastic causes, the commonest lesion is carcinoma of the sigmoid colon with carcinoma of the rectum and then carcinoma of the bladder next in order. Other pelvic carcinomas such as those arising from uterine cervix or ovary have occasionally been reported as the cause. The incidence of adherence to the bladder and of fistula formation in malignant diseases of the bowel in cases from St. Mark's Hospital are shown in Table I. It is perhaps of interest that adherence to the bladder (and by that is meant adherence to such a degree that removal of part of the bladder is necessary) is one and a half times more common in sigmoid growths than in rectal growths, while actual fistula formation is five times as common. Note also the sex difference, naturally greater in rectal growths.

*Pathology* (Fig. 1).—The simplest type of vesico-intestinal fistula is a communication

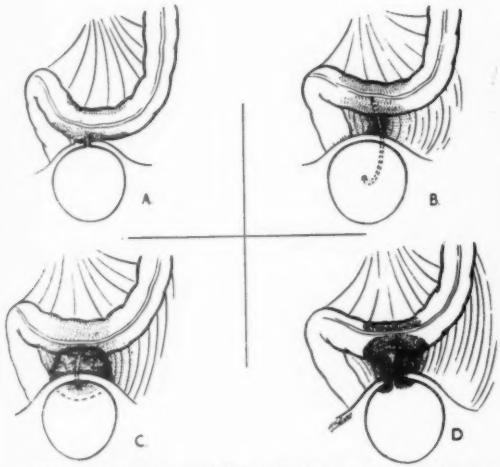



FIG. 1.—Possible pathology leading to vesico-intestinal fistula. A, Direct track. B, Tortuous indirect track. C, Intervening abscess cavity. D, Neoplastic infiltration.



FIG. 2.—Resected specimen showing growth of colon erupting into vesical cavity.

between bowel and bladder with a short direct track, due usually to an infected diverticulum in the sigmoid colon lying on the dome of the bladder (Fig. 1A). In other cases the track may be longer or more tortuous, perhaps tracking into the mesentery of the sigmoid and following thickened peritoneal folds to open into the posterior bladder wall at a lower level (Fig. 1B). Not infrequently there may be an abscess cavity intervening between bowel and bladder which varies considerably in size and may contain only a few minims or several ounces of pus (Fig. 1C). This intervening abscess was first mentioned by Chavannaz in 1897 and called by him the "foyer intermédiaire". The presence of such an abscess cavity adds greatly to the difficulties of operation, and the size and fixity alike make it difficult to tell, even at operation, if the primary lesion in the bowel is inflammatory or neoplastic. It is perhaps worth emphasizing that, even when the primary lesion in the bowel is neoplastic, the actual fistula into the bladder may be only the result of secondary infection and not necessarily an indication of invasion of the bladder by growth. Sometimes, however, malignant cells may grow along the fistulous track and erupt into the bladder (Fig. 1D).

An ileo-colic fistula is sometimes present as well as the vesico-intestinal one. This may occur in cases of diverticulitis or in carcinoma of the colon, and the presence of this second fistula accounts for some, at least, of the failures to improve after proximal diverting colostomy. In cases of Crohn's disease, the presence of an ileo-colic fistula in addition to the vesico-intestinal fistula between diseased ileum and bladder seems to be particularly common, being reported in many cases in the literature and occurring in each of the two cases of vesico-intestinal fistula in Crohn's disease which I have seen.

The changes in the bladder seem to follow a fairly definite pattern with an initial, intense cystitis which then partly settles. There is always more œdema in the neighbourhood of the fistula, and often granulomatous polyps may occur in that part of the bladder. These polyps may even be mistaken for a primary neoplasm of the bladder, especially if the view is poor and the history of pneumaturia is not volunteered by the patient. In most cases the

condition, untreated, will lead to chronic cystitis, a contracted bladder, possibly stone formation and finally ascending pyelonephritis and death. All writers emphasize the bad prognosis of untreated cases, though there may be some confusion here in that many of the deaths in the past were probably due to malignant disease rather than to the presence of the fistula itself. Occasionally a remarkable tolerance of the bladder seems to develop, the patient remaining in good health with minimal symptoms for many years, and with a nearly normal bladder on cystoscopy.

The most important point in the *diagnosis* of vesico-intestinal fistula is the symptom of pneumaturia, with fæcaluria and symptoms of cystitis as close seconds. Other causes of pneumaturia such as certain bladder infections associated with glycosuria, and instrumentation of the bladder, are well recognized but are rare. In most cases seen in surgical practice, however, pneumaturia means a vesico-intestinal fistula until proved otherwise, and is said to occur in 90% of cases but, surprisingly, is not always volunteered by the patient. The passage of urine *per rectum* is much less common. Confirmation of the presence of a fistula can usually be obtained by certain urine tests which were mentioned by Dr. Dukes twenty years ago (Dukes, 1938), such as examination of the centrifuged deposit for fæcal debris and muscle fibres, and culture of the urine for spore-bearing anaerobes; but it is possible for the urine to be sterile in the presence of a small fistula that yet allows air to enter the bladder.

Of particular interest to this Section are the symptoms that may occur before a fistula develops. Tables II and III give an analysis of the cases at St. Mark's and elsewhere.

TABLE II.—VESICO-INTESTINAL FISTULA

*Diverticulitis:* 12 patients { M. 9 / F. 3.

*Age:* Oldest: 71. Youngest: 38. Average: 61 years. Average in men: 55. In women: 68.

*Length of history preceding pneumaturia (or diagnosis):* Longest: 17 years. Shortest: 4 months. Average: 3 years.

*Symptoms preceding pneumaturia (or diagnosis):*

| | |
|---|---|
| Urinary only | 3 |
| Urinary preceding bowel | 3 |
| Of diverticulitis (acute attack) | 3 |
| Urinary and bowel together | 1 |
| Vague abdominal pain | 2 |

TABLE III.—VESICO-INTESTINAL FISTULA

*Carcinoma of sigmoid:* 6—all male.

*Age:* Oldest: 75. Youngest: 42. Average: 57 years.

*Length of history preceding pneumaturia (or diagnosis):* Longest: 15 months. Shortest: 1 month. Average: 3 months.

*Symptoms preceding pneumaturia (or diagnosis):*

| | |
|---|---|
| Urinary symptoms only | 1 |
| Bowel symptoms only | 5 |

Table II shows the cases of diverticulitis; there were 12 patients, 9 men and 3 women. I would like to emphasize the age incidence of the condition, and to draw attention to the rather peculiar difference in the average age in the two sexes. I think it is important to realize that diverticulitis and its complications is a disease commonly seen in the 50s, and is not a disease of old people, and the youngest patient was a man of 38. The patient with a seventeen-year history (of recurrent cystitis) was a personal case, aged 56 at operation, his symptoms having started at the age of 39. I would like particularly to draw attention to the fact that in 6 out of these 12 cases the symptoms were only urinary for a varying time preceding the development of the fistula.

In the cases due to carcinoma (Table III) the age was roughly the same, but the history was predominantly of bowel symptoms, and prodromal urinary symptoms seem to have been less common. However, one patient in this group had frequency and dysuria for five months before pneumaturia developed, with no other symptoms referable to the growth in his bowel.

Diagnosis, to be complete, can be considered under the headings shown in Table IV.

TABLE IV.—VESICO-INTESTINAL FISTULA (*after* Parham and Hume, 1909)

Diagnosis ..
- the condition
- the location { in bladder / in bowel
- the cause
- whether direct or indirect

First, the diagnosis of the presence of a fistula usually means confirmation of the pneumaturia. Harrison Cripps (1888) advised that the patient should be observed while passing water in a hip bath, and while a hip bath is no longer essential, the principle remains excellent. If there is any doubt, passing a catheter and allowing it to drain under water is often a simple ward test which gives much information. If pneumaturia is intermittent, it can sometimes be induced by inflating the bowel with air. At St. Mark's Hospital, all the patients are routinely sigmoidoscoped on admission, and as a result the presence of a vesico-intestinal fistula has sometimes been dramatically demonstrated during or shortly after this examination.

tion. If a vesico-intestinal fistula is suspected, a sigmoidoscopy with air inflation may confirm its presence. The location of the fistulous openings in the bladder and in the bowel and the cause of the fistula are matters for clinical and cystoscopic examination, including a bimanual palpation, and for X-rays. Sigmoidoscopy is not always successful in reaching the lesion, though it should always be done. X-rays are seldom able to show the fistula, but may be helpful in showing the nature of the disease in the bowel. Differential diagnosis between a growth in the sigmoid and diverticulitis is not always easy, however, and indeed the conditions may co-exist.

### Treatment

Treatment, naturally, depends on the cause of the fistula and is best discussed under three headings: (1) The treatment of those cases due to disease in the rectum or colon, whether inflammatory or malignant. (2) The treatment of those cases due to Crohn's disease of the terminal ileum. (3) The treatment of traumatic cases.

*Cases due to disease in the sigmoid colon and rectum.*—The aim in every case is a resection of the diseased bowel with separation from the bladder, if necessary removing part of the bladder wall, sound closure of the bladder and then restoration of bowel continuity. However, this aim is not always possible to achieve. Sometimes the patient's general condition is such that any major operation would prove hazardous, and sometimes a growth may be considered inoperable. Then the best one can do is to establish a proximal colostomy, in the sigmoid colon if possible; if not, in the transverse colon. This is usually, but not always, effective, and there are many cases reported of urinary symptoms continuing after the establishment of a good proximal colostomy. However, in most cases it is satisfactory, but it is important that it should be a defunctioning colostomy with adequate separation of the two ends of the bowel. Simple separation and suture of the two viscera involved in a fistula without resection of the diseased part is seldom satisfactory, has a high recurrence rate, and is not worth doing.

In the majority of cases, resection of the diseased part of the bowel is possible. Resection and anastomosis may be easy if the fistula is a direct one into the dome of the bladder, if only a short length of sigmoid is diseased, and if there is a reasonably long sigmoid colon. In fat patients with short, fat-laden colons, in patients with a more complex fistula opening low down near the trigone, or in those with much fibrosis around the fistula or an intervening abscess cavity, the operation may prove extremely difficult. In these latter cases, it is essential to see and dissect out both ureters, which are otherwise likely to be in danger. In cases of carcinoma, the part of the bladder to which the growth is adherent should be removed, and in very advanced cases the operation of pelvic clearance may be necessary if the growth is to be excised. In inflammatory cases it is usually enough to dissect the colon off the bladder wall, but it is important to try to excise the fibrous tissue so that one can get a good closure of the bladder, which is then drained by an indwelling catheter for ten to fourteen days. At St. Mark's we believe that implantation of malignant cells is an important factor in recurrence after bowel surgery for carcinoma, and take precautions to prevent it. We think that the bladder and cut edges in these cases should be swabbed well with 1 in 500 perchloride of mercury, which is thought to be effective in killing loose malignant cells.

Restoration of bowel continuity is nearly always possible in cases of diverticulitis, as luckily the disease hardly ever affects the rectum, which can be mobilized sufficiently to allow of anastomosis to it of healthy bowel. Sometimes the transverse colon has to be brought down, but anastomosis is nearly always technically feasible and often easy. In 2 of the St. Mark's cases, restoration was not possible. One of these had continuing disease after a transverse colostomy with much perirectal fibrosis and a hopelessly fixed and contracted rectum. The other also had this similar perirectal fibrosis, and furthermore was very fat, a factor which always makes for difficulty in pelvic surgery. Both these cases, in fact, had excision of the rectum performed with a terminal colostomy, but in such cases it may be safer and wiser in certain circumstances to do a Hartmann operation rather than an excision of the rectum.

I would now like to discuss briefly the rather controversial question of whether these operations should be done in one stage or whether a three-stage procedure, that is, transverse colostomy, resection, closure of colostomy, is preferable. Several cases in this series were done in one stage, and there is no doubt that in certain cases the operation may be technically easy and a one-stage operation perfectly safe. Nevertheless, I believe (and with this I think that my colleagues at St. Mark's would agree) that it is usually wiser to do a preliminary transverse colostomy. Even in the easy cases, this does give a slight extra margin of safety, while in those patients with severe urinary symptoms it usually allows the urinary infection to be rapidly overcome and the general condition of the patient to improve. Moreover, the defunctioned bowel can be rendered clean and the further hazard of fæcal soiling following a difficult dissection can be avoided. In cases with much inflammation, it allows œdema to settle, and may considerably reduce the size and fixity of any mass. The interval between

the establishment of the colostomy and the resection must vary, of course, with the particular case, but there is probably rarely any advantage to be gained by waiting longer than six weeks, and very long delays may allow of increased fibrosis around the sigmoid and upper rectum, and may make dissection and anastomosis more difficult. A staged operation is probably wiser even when one is dealing with a carcinoma, though here the interval should be as short as is reasonable, possibly two to three weeks, as this time usually allows for cleansing of the bowel and overcoming of the urinary infection. A short delay of this duration is unlikely to make any difference to the ultimate prognosis of the growth and does, I think, reduce the risk of a resection.

There has been 1 death in the 12 cases due to diverticulitis at St. Mark's; this case was done in one stage and we think his death might have been avoided by staging. All the other cases did well and have remained well. There was also 1 post-operative death among the 6 cases due to carcinoma, and 1 was inoperable; but the remaining 4 cases treated by resection have all remained well for one and a half, two, five and six years respectively. This is rather surprising but encouraging, and shows that a determined attempt at removal of these tumours is justified. Fig. 2 is a photograph of a specimen of one of these patients, operated on by Mr. Henry Thompson, showing the cuff of bladder wall with the growth erupting into the vesical cavity. The growth was of high malignancy and showed both lymphatic and venous invasion, and yet he has remained well for six years to date.

*Cases due to Crohn's disease.*—This subject has been well reviewed by Williams (1954). The disease is predominantly one of young people and must always be considered when urinary disorders occur in such people because, as in cases of diverticulitis, the intestinal symptoms may be minimal or absent, and the general health may be unaffected. The diagnosis is not always straightforward, even when suspected, and X-rays do not always confirm a suspected diagnosis. I have only seen two cases of vesico-intestinal fistula following Crohn's disease, and each underwent resection of the diseased bowel with a satisfactory result. Short-circuiting operations, even with exclusion, may not always cure the fistula. The presence of an ileo-colic fistula or an intervening abscess cavity, as previously discussed, are possible reasons for failure to heal after such a short-circuiting operation. I think that if surgery is undertaken it should be with a view to resection.

*Traumatic cases.*—In those cases due to gunshot wounds or perforating foreign bodies, there does seem to be a strong tendency to spontaneous healing. Poole-Wilson (1952) in discussing the bladder injuries seen at the Genito-Urinary Centre in C.M.F. found that in only 2 of the 15 cases where there was association of vesical and rectal injury did a fistula require surgery. It is difficult to know if there is the same tendency to spontaneous cure in the injuries following operations on the prostate and bladder neck as the cases that do heal are seldom reported and only the failures come to notice. 5 such cases have been referred to St. Mark's in the last ten years. They are, of course, of an older age group, and in these 5 cases the average age was 65, the oldest being 79 and the youngest 55. There have been 2 deaths in these 5 cases, 1 before any surgery was undertaken and 1 following an attempt at closure, both deaths being due to pyelonephritis. 2 have been successfully closed, and 1 has had ureteric transplantation into an isolated ileal loop. It seems probable that direct surgery to the fistula should not be undertaken too early, because there is some tendency to spontaneous healing, and because surgical failure is more likely while there is still œdema of the tissues. It is probably wiser to establish an inguinal colostomy and a suprapubic cystotomy as soon as the presence of a fistula is recognized and to wait several weeks before attempting any local surgery even if the fistula persists. Access to these fistulæ is difficult, both from the perineum and from the abdomen, and Mr. Henry Thompson and I tried a fresh approach in 1955. The first case we did together was a great success, and Mr. Thompson has since done another that was equally successful.

(Slides were then shown to illustrate a posterior approach to fistulæ between the rectum and prostatic cavity.)

It is of course still too early to say, on the results of just 2 cases, whether this will be a real advance in the treatment of these difficult cases, but this approach does seem worthy of further trial.

In conclusion, I would again like to express my thanks to my colleagues at St. Mark's, and particularly to Mr. Henry Thompson.

REFERENCES

CHAVANNAZ, G. (1897) *Ann. Mal. Org. gén.-urin.*, **15**, 1176, 1287.
CRIPPS, H. (1888) The Passage of Air and Fæces from the Urethra. London.
CROHN, B. B., GINZBURG, L., and OPPENHEIMER, G. D. (1932) *J. Amer. med. Ass.*, **99**, 1323.
DUKES, C. E. (1938) *Proc. R. Soc. Med.*, **31**, 1286.
PARHAM, F. W., and HUME, J. (1909) *Ann. Surg.*, **50**, 251.
POOLE-WILSON, D. S. (1952) *Brit. J. Surg.* (War Surg., suppl. 3), 476.
WILLIAMS, R. J. (1954) *Brit. J. Surg.*, **42**, 179.

**Mr. J. D. Fergusson** (London):

The material presented has been drawn partly from a large general hospital (the Central Middlesex Hospital) and partly from a smaller urological hospital group (St. Peter's and St. Paul's) during the period 1952–1958. It may, therefore, be taken as representative of the condition as it first presents in general surgical and urological practice, and I am grateful to all my colleagues for their kind permission to include their cases with my own.

On examining the records it soon became apparent that certain criteria were indispensable to a proper diagnosis of fistula and that in some instances cases listed as suffering from this complication had, in fact, no actual communication between the bladder and bowel. Several patients in whom the urine had been described as fæcal or feculent were subsequently found at operation or post-mortem to have no fistulous opening; and the same was true in a few instances where it had previously been considered that watery stools had been contaminated with urine. Nor did the presence of that somewhat grotesque symptom "pneumaturia", even in the presence of bowel or bladder irritability, necessarily confirm the presence of a fistula. It was, therefore, important, in the interests of scientific exactitude, to insist that the diagnosis should be confirmed by at least one of the following criteria:

(1) The passage of intestinal contents in the urine—usually assessed by the presence of muscle fibres or undigested food residue.

(2) The passage of urine *per rectum* (usually confirmed by the urea content).

(3) The actual detection of a fistulous communication either at operation or autopsy.

Applying these rigid criteria the original number of cases reviewed (30 in all) was eventually reduced to 16 (Table I) in all of whom the presence of a fistula seemed to be established

TABLE I.—VESICO-INTESTINAL FISTULA
(Provisional diagnosis made in 30 cases)

| | | | | |
|---|---|---|---|---|
| Diagnosis: Confirmed | | | | 16 cases |
| Excluded | | | | |
| Urethrorectal fistula | | 1 | | |
| Unconfirmed or untraced | | 5 | | |
| No fistula at operation or autopsy | | 8 | | |
| Meckel's diverticulitis | 1 | | 14 cases | |
| Crohn's disease | 2 | | | |
| Diverticulitis | 2 | | | |
| Carcinoma of colon | 3 | | | |

beyond doubt. Of the remaining 14, one had a urethrorectal fistula (and was excluded on topical grounds), 5 patients *may* have had a fistula but failed to satisfy the suggested criteria or could not be traced, and 8 showed no evidence either of a previous or existing communication at subsequent operation or post-mortem.

The 16 established cases of vesico-intestinal fistula were investigated in detail and grouped according to their ætiology (Table II). It will be noted that no examples of congenital

TABLE II.—VESICO-INTESTINAL FISTULA
(16 cases 1952–58)

| Ætiology | Central Middlesex Hospital | St. Peter's and St. Paul's Hospitals | All cases |
|---|---|---|---|
| Traumatic | | | |
| Post-operative | — | 2 | 3 |
| Radiotherapy | — | 1 | |
| Inflammatory | | | |
| Regional ileitis | 3* | 0 | 8 |
| Diverticulitis | 1* | 4 | |
| Neoplastic | | | |
| Carcinoma of sigmoid or rectum | 1 | 1 | 4 |
| Carcinoma of bladder | 1 | — | |
| Carcinoma of prostate | 1 | — | |
| Uncertain | — | 1 | 1 |
| Totals | 7 | 9 | 16 |

*48 cases of regional ileitis and 306 cases of diverticulitis were treated at the Central Middlesex Hospital during the same period (1952–58).

(neonatal) fistula are recorded and that the traumatic cases are restricted to those induced by what might euphemistically be described as "therapeutic accidents". With regard to inflammatory conditions a point of interest lies in the proportion of cases due to regional enteritis. Although this condition has come to be a well-recognized cause of fistula, it has previously been regarded as less common than diverticulitis in this respect. Nevertheless in this series the numbers show a close approximation which possibly assumes greater

significance when the proportion of uncomplicated cases of the two inflammatory conditions is compared.

During the period concerned 48 cases of Crohn's disease were under observation at the Central Middlesex Hospital as against 306 cases of diverticulitis. Fistula into the bladder occurred three times in the former, but was detected only once in the latter. Although the numbers are small they invite speculation as to whether a new trend is occurring in the ætiology of inflammatory fistulæ and whether, in fact, diverticulitis continues to play a predominant role. Personal experience suggests that with antibiotic therapy and selective surgical treatment fistula due to diverticulitis is becoming rarer, although, of course, adherent lesions to the bladder are still commonly encountered. It may also be questionable whether some lesions of the latter type have not in the past been falsely designated as fistulous since the symptoms to which they give rise often closely mimic those in which true communication has become established.

Among the neoplastic causes listed there appears to be a notable dearth of malignant conditions of the bowel which in previous series have constituted a major cause of fistula formation. The figures here, however, are probably misleading since 2 additional cases of carcinoma of the sigmoid in which a fistula was suspected were referred to St. Mark's Hospital for subsequent treatment. Nevertheless it is tentatively suggested that with improvement in early diagnosis and treatment this type of fistula may also be becoming relatively less common.

In order to emphasize the ætiological pattern which I have described the present series has been compared with a comprehensive record of 148 cases compiled by Williams (1954) (Table III). As already indicated the most marked divergence occurs in the inflammatory

TABLE III.—VESICO-INTESTINAL FISTULA

Ætiological Comparison between Present Series (16 Cases) and 148 Cases Collected from Various Sources 1936–54 (Williams, 1954)

| | Collected series (148 cases) | Present series (16 cases) |
|---|---|---|
| Congenital .. | 6 | — |
| Traumatic .. | 22 (post-operative 19) | 3 (post-operative 2) |
| Inflammatory .. | 51 (regional ileitis 8) (diverticulitis 23) | 8 (regional ileitis 3) (diverticulitis 5) |
| Neoplastic .. | 64 (carcinoma of bladder 10) (carcinoma of sigmoid and rectum 44) | 4 (carcinoma of bladder 1) (carcinoma of sigmoid and rectum 2) |
| Uncertain .. .. | 5 | 1 (carcinoma of prostate 1) |

group showing the relative importance of regional ileitis and diverticulitis, and also in the comparatively few cases of sigmoid and rectal cancer included in the present series. The latter discrepancy may be due to the fact that cases of cancer of the lower bowel complicated by fistula tend to become concentrated in special centres thus lending themselves more readily to collective review, and giving rise to a spurious impression of their actual frequency. It would be wrong, however, to draw any definite conclusions from the small numbers in the present series and any suggestion of this nature must remain largely speculative.

Reverting now to the actual cases in the present series, certain points of interest in the symptomatology and diagnosis of vesico-intestinal fistula will be discussed.

In general it may be said that, apart from some traumatic cases where the presence of a fistula is immediately evident from the nature of the injury, diagnosis is commonly delayed until the actual passage of specific contaminants in the urine and fæces. Even in traumatic cases the position may sometimes initially remain obscure, though in some instances the issue may be decided by early exploration. In civil practice the incidence of traumatic fistula is low and the only cases recorded in the present series followed either surgical procedures or irradiation. In one of these a second-stage prostatectomy had been carried out, apparently with some difficulty, and the bladder drained suprapubically in the customary manner. No injury was suspected at the time, but a week later fæces were detected in the drainage and urine was passed *per rectum*. Subsequent rectal examination revealed a large fistulous opening through which the finger could be passed into the bladder. In a second case perurethral resection of the bladder neck for urinary retention in a patient with pernicious anæmia was followed by clot retention and the escape of blood and urine *per rectum* on the fourth post-operative day. The latter finding led to the detection of a small sloughing fistulous aperture on rectal examination. In the third case resection of a tumour near the bladder neck was supplemented by the insertion of radium needles attached to a Foley catheter. This led three months later to the passage of a slough *per rectum* followed by the voiding of urine with the fæces. Fæcal matter also appeared in the urine and the presence of a fistula was confirmed by cystoscopy. It will be noted that in all these cases urine was

readily detected in the stools, in keeping with the view that urinary leakage is usually most in evidence when the fistula occupies a low position in the bladder.

It was a little surprising that these examples represented the total number of traumatic fistulæ (during the period under review) at a urological centre to which difficult and complicated cases are frequently referred. Despite the extensive use of the boomerang needle, tantalum wire applicators and diathermy no fistulæ from these causes were recorded; and radiation necrosis, if it occurred, possibly led to death from other causes before a communication could be established. Nevertheless cases bordering on fistula due to traumatic causes, and presenting with suggestive symptoms are not uncommon, as demonstrated by the following examples:

A youth of 17 was admitted to hospital with a three-day history of severe strangury and rectal tenesmus. No predisposing cause could be elicited at the time but his urine was foul and watery mucus was passed *per rectum*. An X-ray (Fig. 1) demonstrated the presence of two parallel opaque



FIG. 1.



FIG. 2.



FIG. 3.

FIG. 1.—Pseudo vesico-intestinal fistula. Linear streaks indicate 5½-in. penholder in bladder which had perforated the viscus and stripped the adjacent rectal wall without actually perforating the latter.

FIG. 2.—Pseudo vesico-intestinal fistula. Perforation of the cæcum by a nail file (swallowed after leucotomy). The foreign body impinged on the bladder giving rise to urinary symptoms.

FIG. 3.—Pseudo vesico-intestinal fistula. Broken-off guide wire (for hip arthrodesis) lying in relation to cæcum and bladder and associated with urinary symptoms.

lines running vertically upwards in the region of the bladder. These were apparent by virtue of the radio-opacity of the blue paint on a 5½-in. penholder which he had some days previously inserted into the urethra. At operation the foreign body was found to have perforated the bladder and stripped the muscle of the rectal wall without actually effecting a full communication.

In a second case a leucotomized woman swallowed a nail file (Fig. 2). This fact was concealed from her practitioner who was called in only at a later stage when she had developed an abscess above the pubis which was discharging fæces on to the abdominal wall. Her urine was heavily infected and she complained of frequency and dysuria. Removal of the foreign body, which was embedded in an abscess cavity contiguous with the cæcum and bladder, was followed by a discharging sinus which eventually healed. Repeated injections of opaque media failed to show any communication with the bladder, and her urine, which had never contained any actual fæcal constituents, later cleared.

Finally a third patient presented with gross urinary infection and accompanying irritability of the bowel with bouts of watery diarrhœa. A previous arthrodesis of the right hip (Fig. 3) had left him in possession of a fragment of a metal guide which an X-ray showed to be encroaching on the bladder area. Cystoscopy clearly defined the point of the guide, which had caused a pyramidal elevation of the vesical mucosa, but his symptoms were due to the presence of an infected tumour involving the opposite side of the bladder and subsided when this was later removed.

The foregoing cases serve to show how circumstances may sometimes arise leading to a suspicion of traumatic fistula when none in fact exists. The same applies in even greater measure to inflammatory cases where, despite the presence of combined symptoms of bowel and bladder irritability from a contiguous lesion, no actual perforation has occurred. The presence of foul urine and watery rectal discharge offers insufficient evidence alone on which to make a diagnosis and even the additional presence of pneumaturia may be misleading. On the other hand it may be mentioned that where an actual fistula has been proved symptoms may often be insignificant or even conspicuous by their absence. In general, however, it appears that most inflammatory cases give an initial history relating to the primary intestinal lesion which later becomes complicated by the development of symptoms due to bladder involvement. In this respect the time interval varies, but comparison between the two common causes, regional ileitis and diverticulitis, shows that the former usually tends to run a more chronic course. In the three instances of Crohn's disease causing fistula in the present series the interval between the onset of bowel and bladder symptoms was three, thirteen and fourteen years respectively, whereas in the 5 cases of diverticulitis the corresponding periods amounted to one year in 2 cases, and two, three and four years in the remainder. With regard to the sex and age incidence, 2 of the 3 cases of Crohn's disease were male and in all instances the fistula became established before the age of 50. Of the 5 cases of diverticulitis 3 were male and the youngest was 50. There was little apparent difference in the ultimate urological presentation of the two groups, all cases suffering from symptoms of intermittent or persistent cystitis, although in 2 cases these were very slight. Occasional pneumaturia occurred in 4 (2 with Crohn's disease) and definite fæcal contamination of the urine was found in all but one.

It has been suggested that the occurrence of pneumaturia in Crohn's disease always implies extension of the inflammation process to involve the sigmoid. In one of the present cases this was undoubtedly true, but in the other a barium enema failed to show any evidence of colonic disease. In a recent case of Crohn's disease under the care of Mr. D. M. Wallace, the symptoms and cystoscopic appearances strongly suggested the presence of a fistula although no contamination of the urine or fæces was established. Operation revealed a coil of ileum adherent to the bladder with impending perforation, but no involvement of the sigmoid was detected. While on the subject of pneumaturia in inflammatory lesions it must be reiterated that, though often affording strong supporting evidence of fistula, it need not be infallible in this respect. In one of the rejected cases a patient continued to pass "gas" intermittently in the urine for years after a previous short-circuiting operation for presumed ileitis, but subsequent exploration failed to reveal any communication and the resected specimen proved intact. In the absence of diabetes (and of preceding urethral instrumentation) it may be assumed that the cause in this case was produced by fermentation due to an associated cystitis. Conversely, in another case of Crohn's disease where pneumaturia had previously been much in evidence, the passage of "flatus" *per urethram* ceased abruptly after commencing treatment with prednisone. Six months later, however, after withdrawal of the drug pneumaturia recurred and the presence of a fistula was confirmed by fæcal contamination of the urine.

It may be noted that, while all the proven cases of inflammatory fistula showed the presence of fæces in the urine and occasional pneumaturia, in contradistinction to the traumatic fistulæ the appearance of urine in the stools was never conspicuous. Most of the inflammatory fistulæ were small with their orifices partially occluded by œdematous mucosa, and all but one were situated fairly near the apex of the bladder. It is probable, therefore, that urinary leakage was slight and the re-absorptive function of the bowel prevented any undue collection of fluid in the rectum.

Turning now to the small group of neoplastic cases, similar observations to the foregoing apply in the case of growths originating in the sigmoid. Preliminary symptoms usually relate to the primary lesion of the bowel, being followed later by evidence of bladder irritability and fæcal contamination of the urine. Obvious leakage of urine *per rectum* is more likely in rectal growths where the fistula is lower, and again pneumaturia, though highly suggestive, may not be confirmatory. The latter symptom was much in evidence in a rejected case suffering from a high carcinoma of the rectum and coexisting cystitis. Removal of the rectum with an area of adherent bladder showed that the growth was entirely confined to the bowel and that all surrounding changes were inflammatory. No fistulous communication could be demonstrated.

Of the proven neoplastic cases in the present series 2 were male patients suffering from cancer of the sigmoid. Fæces were demonstrated in the urine in both cases and the underlying cause was established by barium enema although this failed to show a communication with the bladder. Of the remaining 2, one had an extensive bladder neoplasm which ulcerated into the rectum and the diagnosis of fistula subsequently seemed assured when the patient passed a plum stone *per urethram*. The final case was unusual in representing a vesico-prostato-rectal fistula due to cancer of the prostate. Actual invasion of the rectum is rare in this disease and the patient presented with what appeared to be a mundane pile at the anal verge (Fig. 4).

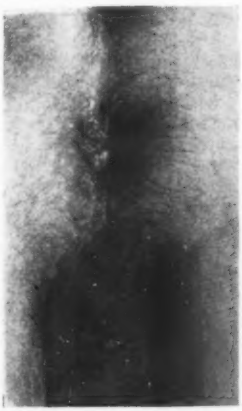


FIG. 4.—Prostatic cancer presenting *per anum* with vesico-prostato-rectal fistula.

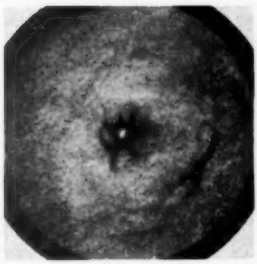


FIG. 5.—Cystoscopic appearances of vesico-intestinal fistula due to diverticulitis coli.

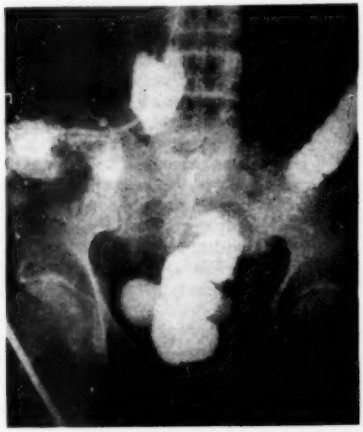


FIG. 6.—Barium enema showing fistulous communication between colon and bladder in a case of diverticulitis coli.

Before considering the last case in the series (in which the ætiology remains uncertain) brief reference may be made to the value of ancillary investigations in establishing the presence or site of a fistula. These fall into two categories, firstly methods of endoscopic examination by sigmoidoscopy or cystoscopy and, secondly, the introduction of various media into the cavities concerned with a view to demonstrating leakage. In many instances the additional information gained by these measures is somewhat disappointing for, although they may clearly show the presence of a primary lesion, the actual existence of a fistula often remains in doubt. Allusion has already been made by Mr. Lockhart-Mummery to the place of sigmoidoscopy in demonstrating a fistula but in the present series this examination contributed little to what was already known. Excluding traumatic cases in which the lesion was self-evident, cystoscopy was also of somewhat dubious value and in only one case where fæcal contamination of the urine had already been confirmed was it possible to obtain visual evidence of the discharge of flatus and fæces (Fig. 5).

With regard to X-ray investigations, barium meal examination consistently defined the existence of regional ileitis when this was present though in no instance was the actual fistula demonstrated. In the 7 cases of lower bowel involvement by diverticulitis or cancer the causative lesion was also readily diagnosed by barium enema, but in only one did the contrast medium flow into the bladder (Fig. 6). The injection of effervescent methylene-blue solution by a rectal tube was ineffective in demonstrating a fistula into the bladder in one case of diverticulitis, while the reverse route of injection, including cystography, was only helpful once in this series.

In the last case in the series the diagnosis of fistula was suggested in a somewhat novel manner.

A woman of 56 was admitted to St. Peter's under the care of Mr. Wallace complaining of urinary frequency and incontinence. Two years previously she had sustained a severe head injury and had been taken to another hospital where she remained unconscious for several days and was incontinent. No details of treatment during this period are available but at cystoscopy a month later she was found to have a severe necrotising cystitis, and large sloughs were passed *per urethram*. One year later she complained of muscle fatigue and was examined in a neurological clinic without any cause being detected. At about the same time she began to suffer from diarrhœa which continued with her urinary symptoms until her admission to St. Peter's. Cystoscopy revealed a small contracted

bladder which would not distend and which remained inflamed and œdematous. No fistula was noted. Persistence of the diarrhœa led to further investigation by Dr. A. R. Harrison who remarked that, despite superficial indications of small bowel disease, these seemed unlikely to account for all her symptoms. The blood electrolyte pattern, however, showed a striking resemblance to that following ureteral transplantation and he became convinced that she had a vesico-intestinal fistula. He further suggested that the muscle weakness might have been due to continued potassium loss. Following abortive attempts to demonstrate a communication by barium enema and cystography, the presence of a cæco-vesical fistula of undetermined origin was established at operation. After resection and closure of the fistula her blood chemistry reverted to normal and muscle power was restored.

REFERENCE.—WILLIAMS, R. J. (1954) *Brit. J. Surg.*, **42**, 179.

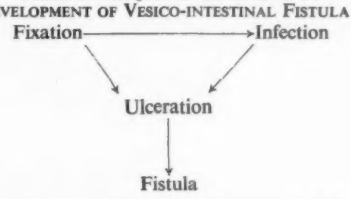
**Mr. C. G. Scorer** (Uxbridge): *Urinary Symptoms in Bowel Disease*

An acquired vesico-intestinal fistula, unless it be traumatic, is the final stage of a disease process which has been advancing more or less insidiously during preceding weeks or months. Symptoms of one kind or another almost invariably precede the fistula and, in this connexion the older writers spoke of "bladder irritability". I want to try to analyse this term.

The structure of the peritoneal membrane is such that the surface of the intestine normally glides over the outer surface of the bladder with a smooth and easy motion. Once, however, disease has destroyed the smoothness of the bowel by inflammatory exudate it can begin to fix itself to the bladder wall. With fixation symptoms may appear. But before attributing bladder symptoms to the bowel it is important to be sure that the cause of the trouble does not lie within the bladder itself or, more important, at its outlet in the form of some obstruction. At the age when bowel disease is commonest, obstruction to the outflow of urine is also most likely to be found. This must be carefully excluded in every case before the bowel is incriminated.

There are four stages of bladder involvement by the intestine (Table I):

TABLE I.—SEQUENCE OF EVENTS IN DEVELOPMENT OF VESICO-INTESTINAL FISTULA




It is presented in this way because the initial involvement of the peritoneal surface of the bladder may be either by fixation or by infection. Each stage would appear to have certain specific symptoms (Table II), although one may merge slowly and imperceptibly, or rapidly and dramatically, into the next as the disease progresses. The symptoms are cumulative and all may be there at one or other time in the fully developed vesico-intestinal fistula.

TABLE II.—SYMPTOMS ASSOCIATED WITH PREFISTULAR STAGES AND WITH FISTULA

| | |
|---|---|
| (1) *Fixation* .. .. | Difficulty with micturition<br>Recurring attacks of frequency |
| (2) *Infection* .. .. | Persistent frequency and urgency<br>Hypogastric pain |
| (With abscess) | Urinary retention |
| (3) *Ulceration* .. .. | Hæmaturia |
| (4) *Fistula* .. .. | Passage of gas and fæcal matter |

(1) *Fixation.*—At some time in the course of a disease, be it carcinoma, diverticulitis or ileitis—to take the three commonest—the affected part of the bowel becomes stuck to the peritoneal surface of the bladder. If the area of fixation is small there will be no symptoms; if large, movement of the bladder wall is impeded and the patient notices a difficulty with micturition.

For instance, in 2 cases of carcinoma of the sigmoid colon the growth was adherent to the peritoneal surface of the bladder over an area of approximately 4 sq. cm. In removing the growth a partial cystectomy was performed. No penetration of the peritoneum by growth had occurred. In neither case were there urinary symptoms.

If, however, the fixation area is large the bladder wall is tethered, normal muscular contraction is impeded and the patient experiences difficulty especially in starting micturition. A man of 54, referred for urological opinion on account of urinary difficulty, found he could

not easily start the act and was obliged to attempt micturition more frequently than normal. Cystoscopically the bladder mucosa was normal. At laparotomy he had a carcinoma of the lower pole of the cæcum adherent to the peritoneal surface of the bladder over a wide area.

By the time extensive fixation has occurred inflammation is probably also extending across to the bladder, so this first group of cases where there is fixation passes over into the second group where infection is the most striking feature. If the bladder is prevented from contracting effectively because the bowel is fixed to it urine is retained and may become infected leading to symptoms of frequency and what is described as "bladder irritability".

Fixation of bowel to the bladder may be of long duration with persisting symptoms. A man of 52 presented with abdominal pain and recurring attacks of urinary frequency. Operation revealed an extensive ileitis with the lower ileum densely attached to the upper surface of the bladder. A partial cystectomy with a wide ileal resection was performed. The interest of this case lay in the fact that at an exploratory laparotomy twelve years before the ileum was *then* adherent to the bladder. In all those years he had suffered from difficulty with micturition and recurring frequency. Cystoscopy had always revealed a normal bladder mucosa.

(2) *Infection.*—If the pathological process which causes the fixation of bowel to bladder advances, infection of the bladder wall supervenes, the area of attachment increases and œdema of the submucosa of the bladder occurs. A comparable process occurs when a pelvic abscess is beginning to break into the rectum. With the finger-tip a smooth, swollen œdematous area is felt. We cannot feel the mucosa of the bladder but we can see it and the swelling may be such that the wall is thrown into glistening folds.

There is now a continuing frequency of micturition which is both urgent and painful. In addition the patient experiences a characteristic hypogastric pain or discomfort and a feeling of weight.

A man of 68 was cystoscoped several times because of frequent and painful micturition. The bladder mucosa was always more or less inflamed but there was no bladder neck obstruction, and with antibiotic treatment the symptoms subsided—only to recur very soon. Eventually he was admitted urgently to hospital with symptoms of a vesico-colic fistula and it was too late to help him further. Autopsy revealed a cancer of the anterior wall of the rectosigmoid junction just beyond the reach of the finger (Fig. 1).



FIG. 1.—Carcinoma of rectosigmoid junction infiltrating and fixed to posterior wall of bladder (prefistular stage).



FIG. 2.—Fleshy "tumour" in the bladder surrounding a vesico-colic fistula due to diverticulitis.

A recurring or persistent bladder irritability in the absence of bladder neck obstruction should suggest the possibility of an extravesical cause. If the cystoscope gives no help the bimanual examination in the relaxed patient must not be forgotten, for the fingers of both hands will always detect between them the inflammatory mass adherent to the top of the empty bladder.

Infection may be mild and resolve spontaneously as in certain cases of diverticulitis. The bladder symptoms will then also resolve and may not recur. On the other hand infection may progress to abscess formation in which case symptoms are severe and may be very distressing.

Three things may happen to the abscess. It may resolve, it may discharge into the bladder or it may discharge into the rectum or elsewhere. If the abscess discharges into the bladder a fistula is established but provided the cause is not malignant disease or a chronic progressive inflammation it may heal spontaneously. Even with diverticulitis, however, the fistula is often permanent. The abscess often finds its way into the rectovesical pouch. Here it may distort and inflame the bladder causing not merely a difficulty with micturition but a urinary retention.

A man of 62 was admitted with severe lower abdominal colicky pains of eight days' duration and a recent acute retention. A diagnosis of diverticulitis with abscess formation was made and a Riches' suprapubic catheter inserted. Three days after admission the abscess was evacuated spontaneously from the rectum. Normal micturition returned within a further few days and the Riches' catheter was removed. Eight months later the diseased segment of pelvic colon was removed; it was found to be stuck to the back of the bladder but was not then inflamed.

It is surprising, however, how seldom a pelvic abscess—even a large one—causes urinary symptoms but it may do so; the inflamed pelvic appendix, especially in children, can present with bladder irritability and even urinary retention.

(3) *Ulceration* is but a stage farther than the last group, bladder wall infection. The mucosal surface breaks down. In addition to the other symptoms already mentioned, hæmaturia may occur.

A woman of 68 had a carcinoma removed from the pelvic colon and a left iliac colostomy was performed. Three years later she presented with a symptomless hæmaturia. Cystoscopy revealed a carcinomatous ulcer on the left lateral wall; a second bowel carcinoma had occurred and had penetrated the bladder wall. There was no fistula even up to the time of her death eight months later—this was doubtless because of the colostomy above.

A man of 55 presented with a history of hæmaturia and on cystoscopy was found to have a soft fleshy "tumour" covered with blood clot in the left wall of his bladder (Fig. 2). It was only later that he began to pass gas and fæcal matter through the urethra. At biopsy the tumour was found to consist of granulation tissue only. The condition was due to a diverticulitis of the pelvic colon.

(4) *Fistula.*—With the establishment of the fistula the change of symptoms may be very slight, alarmingly sudden or of any intermediate degree.

During a mild attack of frequency fæcal particles may be noticed in the urine and bubbles of gas escape from the bladder at the end of micturition, but often this merely arouses a mild curiosity in the patient and causes him neither discomfort nor anxiety. On the other hand, at the end of a bout of severe urinary frequency with lower abdominal pain the bladder wall breaks down to admit fæces and the patient experiences the terrible distress of a scalding micturition with strangury.

The variability of symptoms with fistula is important. Clearly the degree of bladder irritation depends on the quantity and quality of the fæcal leak from the bowel. Gas or a little solid fæcal matter may be tolerated with complete unconcern but fluid fæces whether from the small or large bowel may have agonizing effects.

A fistula can exist for years or be a rapidly fatal, or terminal, event. Harrison Cripps (1888) quotes a case of fistula that lasted twenty years. One of our own lasted four years. He had recurring attacks of urinary frequency and difficulty and it was only when we found what appeared to be a piece of cabbage in the bladder that we became suspicious. Even then we did not believe the evidence before our eyes but having felt a swelling above the bladder made a diagnosis of urachal cyst. At laparotomy a small and narrow fistula was found between the lower ileum and the top of the bladder due to Crohn's disease.

But a fistula may be a rapidly fatal or terminal event especially when due to carcinoma. In this case it is the primary disease which has reduced the patient's vitality. The exacerbation of bladder irritability when the fistula occurs merely hastens the end of an already miserable existence.

The majority of patients with fistula, however, become reasonably tolerant of their disability provided urine can escape from the bladder. As is well known the bladder mucosa may appear surprisingly normal even though fæces are constantly discharged over its surface. If bladder neck obstruction is present the patient sooner or later succumbs to a pyelonephritis.

One further point remains to be mentioned. If a patient with urinary frequency and pain is known to have bowel disease—say diverticulitis—is there reason to believe that the urinary symptoms are caused by the bowel disorder even though an organic connexion of the one with the other is improbable?

The mere presence of a lower abdominal or pelvic discomfort may cause a patient to empty the bladder more frequently than normal and urinary symptoms can, at times, disappear after removal of a diverticulous pelvic colon. But this proves nothing.

Considering how well insulated the bladder is from the bowel it seems reasonable to assume that it is only when the peritoneal coat of the bladder is involved that symptoms occur.

REFERENCE—Cripps, H. (1888) The Passage of Air and Fæces from the Urethra. London.

# Section of Orthopædics

President—J. A. CHOLMELEY, F.R.C.S.

[*June* 28, 1958]

MEETING AT THE ROYAL NATIONAL ORTHOPÆDIC HOSPITAL, STANMORE

## Osteotomy in the Treatment of Congenital Dislocation of the Hip

[*Abridged*]

By DAVID TREVOR, M.S., F.R.C.S.

*London*

THIS short paper deals with rotation osteotomy, combined where necessary with a wedge adduction osteotomy, a curative procedure in contrast to the Lorenz bifurcation or the Schanz osteotomy, which are palliative measures dealing with symptoms arising from unsuccessful primary treatment.

The occurrence of anteversion of the femoral neck has been known for a long time; the recognition of its significance is more recent and its treatment more recent still. It must be conceded that orthopædic surgeons abroad have been more alert in this respect than their British contemporaries. Whether the torsion is a primary deformity, as suggested by Badgley (1943), or whether it is a secondary deformity matters little; it is, however, essential that it shall be recognized, its significance appreciated, and the necessary steps taken for its correction. Uncorrected anteversion is the commonest cause of redislocation either by forward displacement of the femoral head in severe cases or by lateral displacement in moderate degrees of torsion, the femoral head maintaining an unnatural pressure on the acetabular roof which causes arrest of its development.

Many methods for estimating the amount of anteversion have been described: Rogers (1931) described a procedure in which the femoral neck angle was radiographed in different planes and by a complicated mathematical formula the angle of torsion was deduced. Dunn (1952) described an experimental method and showed how the position of the limb when radiographed could influence the estimation; a similar method had been used at the Royal National Orthopædic Hospital. It has been maintained by Rogers (1934) that the angle of anteversion can be readily determined by screening the patient on her face: the affected limb is externally rotated until the shadow of the head, neck and shaft are in one straight line: the amount of external rotation necessary is subtracted from 90 degrees and this gives the angle of torsion. All these methods are inaccurate and fortunately are unnecessary.

The presence of anteversion can be diagnosed clinically; thus, with the knee pointing forwards the femoral head can be felt in the groin whilst the most prominent part of the great trochanter is felt posteriorly in the buttock: on internally rotating the hip the femoral head is no longer detectable and the most prominent part of the trochanter is felt laterally in the thigh. Confusion can arise with an enlarged femoral head but the trochanter would be felt in its normal position. A plain radiograph helps. It should be noted that with much anteversion, the neck is foreshortened and the radiographic appearances resemble those of severe valgus deformity; the foreshortening of the femoral neck disappears with the hips internally rotated (Fig. 1). Both anteversion and valgus deformity can occur



A B

FIG. 1.—A, Radiograph of child's hip with severe degree of anteversion. The neck is foreshortened. The head points almost vertically. This could be confused with valgus deformity but on rotating the hip-joint internally, B, foreshortening of the neck disappears, the head is pointing towards the opposite sacro-iliac joint, and Shenton's line is restored.



A B



C

FIG. 2.—A, Femoral neck appears to be almost in a straight line with the femoral head and shaft, indicating a severe degree of anteversion with possibly a valgus deformity as well; B, Hips internally rotated fully. The femoral neck is still somewhat foreshortened. The femoral head points to the ipsilateral sacro-iliac joint, while Shenton's line is not restored. There is thus a valgus deformity as well as anteversion. C, Results after rotation osteotomy with varus wedge resection. The femoral head now points to the contralateral sacro-iliac joint and Shenton's line has been restored.

together—but in these circumstances, when the hip is fully internally rotated, Shenton's line is not restored and the femoral head does not point to the *contra*-lateral (as it should do) but to the *ipsi*-lateral sacro-iliac joint (Fig. 2). It is possible by such clinical means, aided with plain radiographs, to diagnose and classify anteversion into mild (up to 30 degrees), moderate (30 to 60 degrees) and severe (60 to 90 degrees).

Can anteversion be corrected by closed methods? At one time at the Royal National Orthopædic Hospital it was thought possible in the very young, by diminishing the amount of internal rotation of the hip-joint in successive plasters, to mould the still relatively plastic femoral neck against the anterior rim of the acetabulum and capsule; the results were disappointing. All instances of anteversion, moderate or severe, require operative treatment for correction, but before it is undertaken two conditions must be fulfilled: (1) the head of the femur must be reduced into the acetabulum and (2) the hip-joint must be capable of being internally rotated. It is valueless to do a rotation osteotomy otherwise. The procedure is a final step at the end of a surgical programme.

### *Operative Technique*

The femoral shaft is approached laterally, the skin incision directed forwards; this allows easier suturing of the wound at the end of the operation when the knee has been rotated outwards to the neutral position. The femur can be divided in the subtrochanteric or supracondylar regions; the advantages of the former site are (1) easy accessibility, (2) division of the bone is nearer the site of deformity, (3) convenience for internal fixation and (4) any valgus deformity can be corrected at the same time. The supracondylar osteotomy has the advantage that the hip-joint need not be immobilized post-operatively, a toe-to-groin plaster being adequate. The femur should be transfixed by a Steinmann's pin at the base of the great trochanter and the hip-joint held firmly in full internal rotation. Two distinguishing marks are made on the femur; it is then divided cleanly, without any spikes, between these marks which help to indicate the amount of derotation effected. After the femur has been divided the lower fragment is rotated outwards until the knee is in the neutral position. A plate and 4 screws are used for internal fixation; alternatively Steinmann's pins transfixing the two fragments can be incorporated in the plaster. Immobilization in a full single hip spica for eight weeks has proved adequate.

Where there is in addition a valgus deformity, this is dealt with after derotation by removing a small wedge with the base medially from the upper end of the lower fragment; the limb is then adducted to close the gap, and a strong stainless steel plate, bent as necessary, is applied. On bringing the limb back to the neutral position the femoral head is brought down into its correct position in the acetabulum (Fig. 3).

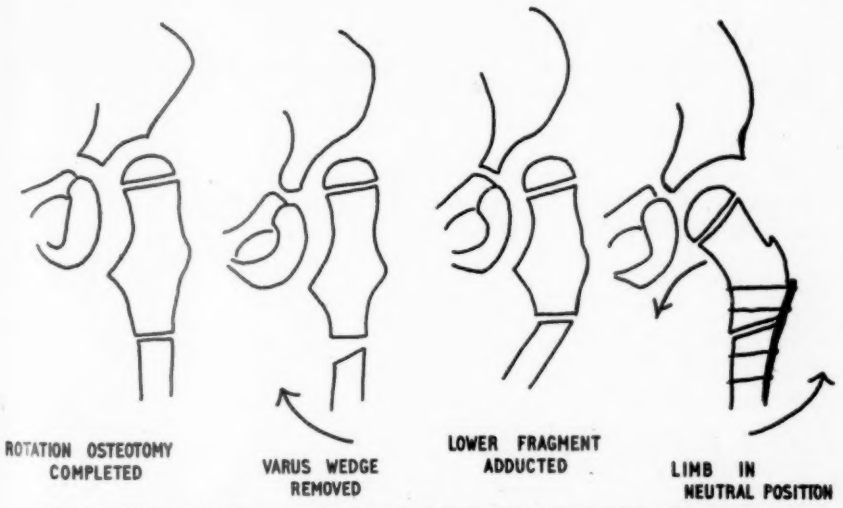



FIG. 3.—Diagram to illustrate the method of correcting simultaneously anteversion and valgus deformity of the femoral neck.

The first rotation osteotomy for dislocation of the hip was performed seventeen years ago and since that time it has been employed on many occasions, but not routinely. It is hoped to publish a fuller account of the results elsewhere. The youngest patient operated on was 18 months old and the oldest 12 years. The amount of correction obtained at operation varied from 30 to 90 degrees with an average of approximately 65 degrees. The average age of this series was 4½ years. As mentioned, the osteotomy was the last stage in the treatment and followed on such procedures as open reduction and/or acetabuloplasty, capsular arthroplasty (Colonna), or closed reduction.

There was no sepsis, although on two occasions the wound broke down but fortunately did not become infected. This was due to insufflation into the wound of penicillin with a powder which produced a granulomatous reaction with giant cells, confused erroneously with tuberculosis: removal of the plate became necessary but was delayed for one month, until the osteotomy was reasonably firm, after which the wound healed rapidly. There was no instance of delayed or non-union.

Recurrence of deformity occurred on three occasions and necessitated a further osteotomy; it is possible that insufficient derotation was obtained at the first operation, a fault probably due to the operator and not to the operation. At the end of the operation no internal rotation of the hip should be possible. With time some internal rotation reappears: the speed of this return is unpredictable, some children recovering only 15 degrees after three to four years whilst others regain up to 50 degrees in the same period.

REFERENCES

BADGLEY, C. E. (1943) *J. Bone Jt. Surg.*, **25,** 503.
DUNN, D. M. (1952) *J. Bone Jt. Surg.*, **32B,** 181.
ROGERS, S. P. (1931) *J. Bone Jt. Surg.*, **13,** 821.
—— (1934) *J. Bone Jt. Surg.*, **16,** 284.

---

## AMENDMENT

**Section of Pathology,** May 1958 *Proceedings*, Vol. **51,** No. 5, p. 343. **Dr. Irvine J. Hunter:** *Some Histochemical Aspects of Pædiatric Pathology, with Remarks on Quantitation in Histochemistry.*

In the above paper there was illustrated the staining of the cross striations of skeletal muscle by fast green F.C.F., an acidic dye. Because of reliance upon the assumption that the muscle striations of all animals are similar, and upon the much-quoted results of Dempsey *et al.* (1946) on the staining of muscle with acidic and basic dyes (in monkeys, rats and a newt), it was then stated that fast green stains the isotropic (non-birefringent) segments. Subsequent work has shown this to be wrong (*see* Hunter, 1958). In man, and other animals so far examined, acidic dyes, such as fast green F.C.F., stain not the isotropic but the anisotropic (birefringent) segments. The stained bands in the photomicrograph (Fig. 1) thus represent the Q band, with central paler Qh, (broad band), and the Z line (narrow dark line).

REFERENCES

DEMPSEY, E. W., WISLOCKI, G. B., and SINGER, M. (1946) *Anat. Rec.*, **96,** 221.
HUNTER, I. J. (1958) *Nature, Lond.*, **182,** 1107.

# Section of the History of Medicine

President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bt., C.B., M.A., D.M., F.R.C.P.

[*October* 1, 1958]

## A Manuscript of Benjamin Collins Brodie's Surgical Lectures, 1822; with Some Notes on the History of Stricture and Stone[1]

By Sir ERIC RICHES, M.C., M.S., F.R.C.S.
*Middlesex Hospital, London*

THERE has come into my possession a manuscript copy of the surgical lectures given by Benjamin Collins Brodie in the season 1822–23, one hundred and thirty-six years ago. They were given at his theatre in Great Windmill Street; this was Hunter's School of Anatomy, now the site of the dressing rooms of the Lyric Theatre. The notes were taken by James Taylor of Todmorden Hall. They are beautifully written, quite legible and form the first volume of a complete textbook, having apparently been taken down verbatim. There may be other copies in existence, and there is at least one two-volume set of notes in the library of the Royal College of Surgeons taken by William Hutchinson, a pupil of Everard Home, in 1810, and presented by Charles Hawkins. Comparison of the two sets shows evidence of the correction and revision which Brodie constantly carried out in his lectures and they form the basis of the surgical part of the edition of Brodie's works collected by the same Charles Hawkins and published in 1865, three years after his death. Brodie entered the Great Windmill Street School as a pupil in 1803 at the age of 20, having attended Abernethy's lectures on anatomy two years earlier. In 1808 he became lecturer in surgery, a post which he held for twenty years.

### JAMES TAYLOR

James Taylor was 20 at the time he made these notes; whether they are a fair copy made at the end of the day's work, or whether they were borrowed or bought from another student and recopied is unknown, but they stood him in good stead for he qualified by the L.S.A. in 1824 and became M.R.C.S. in 1825. He lived and practised as a surgeon at Todmorden Hall, at first with his younger brother Joseph Crossley Taylor who died in 1836. They came of a family known as "The Whitworth Doctors". The first of these, John Taylor of Whitworth, had two sons, George and James, and a brother George, who was the father of James Joseph Hague Taylor. James Joseph married the only daughter of Anthony Crossley of Todmorden Hall in 1801 and came to live there until his death in 1810. He had four sons all of whom became doctors. James was the eldest and lived the longest; his brothers John and George each died at the age of 24. James continued to practise at Todmorden Hall until 1853 when he moved to Culverlands, Berkshire, for health reasons. He died there on November 25, 1872, at the age of 70 and was buried in Burghfield Churchyard, near Reading. He was married twice and had ten children one of whom became a doctor and who lived and practised at Todmorden Hall for some years. He was perhaps the most distinguished member of the family gaining the M.D. of Edinburgh with commendation and becoming a J.P. for Lancashire and the West Riding of Yorkshire; he died at Torquay in 1891.

The town of Todmorden lies on the borders of Lancashire and Yorkshire in the centre of the textile industry. Todmorden Hall, the oldest and most interesting building in the

[1]At the end of the meeting Sir Eric Riches presented the manuscript book of lectures to the Library of the Royal Society of Medicine.

town, is typical of the many fine old halls of the West Riding. It was built early in the seventeenth century by Saville Radcliffe on the site of the older mansion of that family and still contains oak timbers from the earlier building. The hall is built of stone in the style of the period, with shapely gables and mullioned windows. During 1925 this fine old mansion became the Head Post Office, the public part of which is a room panelled in oak, with a finely-carved oak mantelpiece, dated 1603, contemporary with the house.

### Benjamin Collins Brodie

Benjamin Collins Brodie, born in 1783, was one of the six children of the Rector of Winterslow, in Wiltshire. He received his early classical education from his father and never went to a public school. He entered St. George's Hospital as a pupil of Everard Home in 1803, the same year as at Great Windmill Street. He was a diligent student who kept written notes of his cases. He became house surgeon in 1804, assistant surgeon in 1808 and full surgeon in 1822, the year of these lectures. He occupied in turn all the highest positions surgery could offer. He was President of this Society, then the Royal Medical and Chirurgical Society, in 1839 and it is said that he was never absent from a single meeting. In 1844 he was President of the Royal College of Surgeons and in 1858 President of the Royal Society. He reigned supreme in the world of surgery for a quarter of a century. It is of his ideas as expressed in the lectures of 1822 that I wish to speak, and in particular of his teaching on some of the diseases of the urinary tract. He says: "Of all the diseases which come under the care of the Surgeon there are none which demand his attention more than those of the urinary organs, for they are productive of great distress to the patient, they often put his life in danger, and if left alone they go on to a fatal termination, but under judicious treatment they may be relieved by art."

#### *Strictures of the Urethra*

Strictures of the urethra were classified as spasmodic and permanent, the former being explained by spasm of the surrounding muscles and demonstrated by human experiment, but the explanation did not seem to be convincing either to Brodie or his student. He writes: "That spasmodick stricture will prevent the flow of urine is proved by many cases. A person has no disease of the urethra—apply a blister in the neighbourhood—the cantharides are absorbed—he cannot make water—you try to pass a catheter and find it stop at the membranous part of the urethra—when the action of the cantharides is over the urine again flows as usual. A person has a difficulty in making water, you pass a bougie and it will not go farther than the membranous part of the urethra—you touch it with caustick and the urine immediately flows in a full stream. That is simply spasmodick stricture which I now describe. If this occurs very frequently it will remain so, and the part will be permanently contracted. The urine, by the action of the bladder, will be driven with force against this contraction; the mucous membrane will be affected with slow inflammation; it then becomes thickened and this is what we call permanent stricture." He recognizes other causes of stricture such as a bad gonorrhœa, the use of too strong an injection, when used too frequently and when thrown up too far, and other diseases where there is a "morbid secretion of urine." The most frequent complications then as now were retention of urine and fistula in perineo, the latter being considered as in some respects a spontaneous cure, and at least a life-saving event. Extravasation of urine was the most feared: "the urine has generally been collected for a long time and is high coloured, putrid and more or less ammoniacal, this being propelled with force into the cellular texture acts like caustick and the parts are destroyed; all these parts, if the urine be allowed to remain, become black and slough. When a black spot appears on the end of the penis your patient will surely die." Brodie's treatment of stricture was by dilatation with a plaster bougie, or by lunar caustic applied through a silver cannula or on a bougie, the method introduced by Hunter; this was a common cause of false passages. Dilatation by metallic instruments was also used, and continuous dilatation by an indwelling gum catheter in cases in which a speedy cure was desired. For acute retention he favoured opium; he did not think much of the warm bath unless the patient remained in it until it produced some degree of syncope; puncture of the bladder from the rectum was the last resort, with a silver cannula left in for twenty-four hours so that the opening remained fistulous and acted as a safety valve when there was any subsequent difficulty.

These were the methods in common use at the time. Treatment of stricture by incision from the perineum was usually reserved for cases of extravasation, but in 1849 James Syme introduced his shouldered staff which was to be passed through the stricture so that an incision could be made on it from the perineum. He claimed that it gave a more permanent cure, but he was strongly criticized by his contemporaries for operating in cases where they thought dilatation would do as well. Syme's method, however, was most useful

in the badly infected cases of the time. There are still some indications for the use of his staff and many present-day hospitals still possess the instrument.

Injection of warm water into the urethra was also advocated, and a Mr. Machell invented an "Anti-Stricture Injector" whereby a stream of water at varying pressure could be forced against the stricture. Puncture of the bladder was usually done from the rectum, but at a meeting of the Westminster Medical Society in 1849 Mr. Benjamin Travers "related a case of prolonged retention of urine caused by permanent stricture in a young man who had not passed urine except by drops for some days. The patient was drawn to the foot of the bed and the skin incised in the mid-line immediately above the pubic symphysis. A straight dropsy trochar and cannula was pushed into and through the anterior wall of the bladder. On withdrawing the trochar the first jet of urine went half across the ward floor. The relief was very decisive, but so sudden as nearly to induce a fatal collapse. The patient was presently restored by a large dram of gin and subsequently recovered." Suprapubic puncture was not, however, generally accepted although in the examination for the F.R.C.S. in 1849 one of the questions was "In any case where puncture of the urinary bladder (male) is deemed expedient, state the grounds of preference to the operation above the pubes or from the rectum." There were seven candidates and all passed, but we do not know their answers.

Other methods for the treatment of stricture were invented in France where first Civiale and later Maisonneuve introduced an instrument for internal urethrotomy. Maisonneuve's urethrotome as modified some years later by Teevan, and again by Thomson-Walker, is still in use to this day. Mechanical dilators of various patterns had a transient life; Barnard Holt of the Westminster Hospital invented a dilator resembling a pointed metal catheter split into two halves except at the point; it was passed into the stricture and a wedge was then driven between the two halves to produce forcible and rapid dilatation. I had a patient in whom this instrument had been used; he came to me in 1938 at the age of 94 having had a stricture since the age of 30; Barnard Holt had stood him against a wall and passed the dilator; after a warning that it would hurt he had cracked home the wedge. My patient admitted that it did hurt, but avowed that his stream was much better afterwards. His stricture, however, recurred and he passed successively into the hands of Sir William Fergusson, Sir Henry Thompson and Sir George Buckston Browne. The last named taught him how to pass his own catheter whereas formerly he used to go to St. George's Hospital in the night where the porter catheterized him. I did an internal urethrotomy and he came regularly for dilatation for the next three years until his death at the age of 97 from cerebral thrombosis; he always appreciated being given a local anæsthetic for the dilatation, which was new to him, but he had the estimable quality of putting complete trust in the doctor of his choice.

*Stone*

In order to appreciate Brodie's views on calculous disease we must look back much farther than the time of these notes, for this complaint is as ancient as any other to which the human body has ever been subject. Cutting for stone was practised by the Egyptians and Hindus in very early times; the operation was known to Hippocrates (460–355 B.C.) for this clause appears in the Hippocratic oath: "I will not use the knife either on sufferers from stone, but I will give place to such as are craftsmen therein." Stones were removed from the bladder by a perineal operation, and for fourteen centuries the procedure known as the Lesser Operation was employed, so named because it only required two instruments, a knife and a hook. About the year 1520 an improved method was introduced in which the bulb of the urethra was opened on a grooved staff along which a gorget or a pair of strong iron conductors could be passed. This became known as the Marian or Greater Operation from the large number of instruments required. It usually involved forcible tearing of the bladder neck and the mortality was high. It was done by travelling lithotomists who were held responsible for their bad results and fined or executed accordingly.

The next advance was the introduction of lateral lithotomy in which the incision was made by the side of the left ischium. Frère Jacques, its originator, was at one time a trooper in a French cavalry regiment. He subsequently acted as a servant to Pauloni, an Italian lithotomist, and in 1688 adopted a semi-religious habit and the title of Frère. He cut for stone in many parts of France, his custom being that as soon as he had performed an operation he would get the spectators to sign a certificate in his favour without waiting to see if the patient recovered; when he had cut all that came his way in one place he hastened to another. He would not concern himself with the after-treatment, saying "I have extracted the stone, I leave God to cure the patient." The bladder was often cut in several places, and the rectum was not infrequently injured. After an unsuccessful year in Paris he lost his reputation and was forced to wander again. In Holland he was instructed in anatomy and as a result his operation was improved to the extent that only the prostate and bladder

neck were cut, with a corresponding improvement in results. He was presented by the magistrates at Amsterdam with his portrait and a set of gold sounds which he is said to have melted down and distributed to the poor.

It was left to Cheselden, who was lithotomist to St. Thomas' Hospital from 1723 to 1727 to improve the technique; he opened the prostatic urethra and operated with gentleness albeit with rapidity and seldom took more than a minute; his record was 45 seconds, and his mortality in 213 cases was 9·3%. The improved operation of lateral lithotomy held first place for over one hundred years and was in vogue at the time of Brodie. It had been used for many famous men and some have left records of their own experiences of it. Samuel Pepys was cut for stone on March 26, 1658, at the age of 26; as the present year marks the tercentenary of his operation perhaps I may be allowed to mention it briefly. It was done at Salisbury Court by Thomas Hollier or Hollyard who had been appointed surgeon for scald heads at St. Thomas' Hospital in 1638, and who in 1643 was chosen as surgeon for the cutting of the stone. It was stated that he cut thirty for the stone in one year, who all lived. This was vouched for by the porter at St. Thomas's, another indication of the important role played by these officials who until recently had the responsibility of deciding whether a night emergency was medical or surgical. Pepys kept the anniversary as a festival afterwards and referred to it nearly every year. Thus on March 26, 1662, he wrote "Up early. This being, by God's great blessing, the fourth solemn day of my cutting for the stone this day four years, and am by God's mercy in very good health, and like to do well, the Lord's name be praised for it . . . . At noon come my good guests. I had a pretty dinner for them, viz., a brace of stewed carps, six roasted chickens, and a jowl of salmon, hot, for the first course; a tanzy and two neat's tongues, and cheese the second; and were very merry all the afternoon, talking and singing and piping upon the flageolette. In the evening they went with great pleasure away, and I with great content and my wife walked half an hour in the garden, and so home to supper and to bed. We had a man-cook to dress dinner to-day, and sent for Jane to help us, and my wife and she agreed at £3 a year (she would not serve under) till both could be better provided, and so she stays with us, and I hope we shall do well if poor Sarah were but rid of her ague." The stone is said by Evelyn to have been as big as a tennis ball, probably corresponding to the modern squash ball. Pepys had a case made for it which cost him 24 shillings which he thought a great deal of money, but it pleased him. He died at the age of 70 and his left kidney was found to contain a nest of seven stones.

Brodie taught that stones could be formed in the kidneys or in the bladder and that sand deposited in the urine was of two kinds, one of a brick-dust red colour consisting of uric acid, the other of a white colour consisting of triple phosphates. He gave alkaline medicines for the red sand and acids for the white, but recognized that overdosage with alkalis would produce the white sand. Stones were more frequent in children than in adults. He knew that foreign bodies in the bladder could form the nucleus of a stone and described the case of a man from the country, a gardener, who relieved the retention of his stricture by passing a flower stalk. One day it broke off and after a time he went to St. George's Hospital where Sir Everard Home cut him for the stone and it was found that about 3 in. of the flower-stalk formed its nucleus. Obstruction from a stricture was a common cause of stone, and he stated that there is no person with a diseased prostate who sooner or later will not have stone in the bladder if he neglects to use the catheter. The symptoms of bladder stone were described in great detail and with great accuracy and this was necessary because the diagnosis was made on the symptoms, especially the pain in the glans penis, and by sounding the bladder with a metallic sound or a gum catheter. Sounding might be necessary four or five times before the stone was found. Rectal examination was useful if the stone was large.

Treatment was medical and surgical. He realized the limitations of medical treatment saying it had been proposed to give medicines by which the stone may be dissolved: "they will dissolve a stone *out* of the bladder but that is no reason why they should do it in the bladder. I have not the smallest conviction of a calculus ever having been dissolved—the symptoms sometimes go off spontaneously." He then quotes cases of the failure of medical treatment including that of a medical gentleman whose symptoms disappeared with alkaline medicine and who published a pamphlet stating that he had been cured of the stone. He died, and on examining his body a large calculus was found. Brodie used the appropriate medicine after operation, however, and claimed that it prevented recurrence of calculi.

Regarding surgical treatment, he gave no details in these lectures of the operative technique of lithotomy but stated that the operation, though generally proper, must not be performed indiscriminately. The contra-indications included a bad state of general health, symptoms of other diseases, a cough, a sallow countenance, disease of the lungs, the liver or any other internal complaint, an abscess in the pelvis or disease in the kidneys

or diseased prostate. "In serious disease of the prostate you should not operate except by the high operation" and he mentioned two persons who died, one immediately and one a few weeks after lateral lithotomy in the presence of prostatic enlargement.

The prognosis was good in children but bad in old people. In the female the urethra was dilated by a sponge tent until the stone could be extracted and operation was avoided if possible. He described how Mr. Thomas took a tooth-pick out of the female bladder by dilating the urethra with a sponge tent.

In writing his autobiography in later years he said that the only operation which gave him any real concern was that of lithotomy, and that from 1835, except in the hospital, he scarcely ever had recourse to it, substituting for it that of lithotrity.

The high operation mentioned by Brodie for use when the prostate was enlarged was suprapubic lithotomy. It was done only sporadically until 1723 when John Douglas published an account of it. Hippocrates had laid it down that wounds of the bladder were mortal, and there was the constant fear of peritonitis. Syme considered that the danger of cutting into the bladder from above the pubis was so great as to render the operation applicable in but very few cases. That it did not find a permanent place in the early nineteenth century was due partly to the development of lithotrity which promised relief from the dread of a cutting operation without anæsthesia.

*Lithotrity*

The earliest systematic attempts to crush a stone in the unopened bladder were made by Jean Civiale in Paris in 1817. In 1820 John Weiss, whose firm still make good lithotrites, produced a stone extractor for Sir Astley Cooper which was successfully used by Brodie and four years later a curved screw lithotrite for Brodie. He used it on a very hard calculus but the stone broke and the pieces separated with so much violence that he thought they would injure the bladder and he decided not to use the instrument in its present form. Civiale's instruments and those of his French competitors showed a gradual development towards the type which is now used, and it evolved by 1833. At the time of these lectures there was considerable controversy on the relative merits of lithotomy and lithotrity, and this continues in some quarters to-day.

In these notes there is no mention of lithotrity, which was then in its teething stages, but Brodie was one of the pioneers and his "Notes on Lithotrity" appeared in 1853. That lithotrity did not find more favour was due, not entirely to its mortality, 1 in 4, or to the difficulty in removing all the fragments, but to the development of anæsthetics.

*Renal Calculus*

Brodie recognized stone in the kidney from the symptoms and gave a graphic description of renal colic. The pain of the passage of the stone was to be relieved by the patient sitting for hours together in a warm hip bath and taking large doses of opium; generally this treatment was sufficient. For stone in the kidney itself he said "there is no cure, at least there is only one case, i.e. where an abscess forms and where it bursts into the loins: this rarely happens, but it occasionally does."

In Brodie's day surgery of the kidney was practically non-existent except for the opening of peri-renal abscesses or large pyonephroses. The first nephrectomy was done in 1869, seven years after Brodie's death, by Simon of Heidelberg. The year 1880 witnessed the first deliberate nephrolithotomy; it was done by Henry Morris, surgeon to the Middlesex Hospital. Such a proposed operation had been previously condemned owing to the risk of hæmorrhage and fistula, and in 1832 Brodie wrote: "Some of the old surgeons have spoken of an operation for the extraction of calculi from the kidney. The proposal is absurd and dangerous if made with reference to ordinary cases of renal calculi where no abscess exists." In the absence of X-rays the diagnosis in Morris's case rested entirely on the history and physical signs. The patient, Maria Mount, aged 19, a domestic servant, was admitted twice and treated medically; after a third attack she was readmitted under Dr. S. Coupland on December 29, 1879. On February 2, 1880, she was anæsthetized with chloroform and Dr. Coupland endeavoured to examine the kidney with his hand passed along the rectum, but in spite of steady and prolonged pressure found it impossible to insert his hand beyond its widest part. She was taken to the theatre at 1.30 on February 11, 1880, for an exploratory operation under chloroform; Mr. Morris opened the right loin and exposed the kidney. With his right forefinger he detected something rounded, the size of the uncut end of a pencil in the kidney. He passed a straight probe-pointed bistoury along his finger, incised the substance of the kidney at its projecting part and removed the stone with his finger. It was a mulberry calculus weighing 31 grams and is preserved at the Middlesex Hospital. The wound healed slowly and after two months there was still a small fistula. She wore an apparatus to collect the urine, made by Mr. Hawksley, but a month later the wound was dry and she made a complete recovery.

*The Prostate*

Brodie described the symptoms of prostatic obstruction and gave a full description of the pathology, particularly of the late cases, but his treatment was confined to the relief of retention. He did, however, recognize the greater risk to life of chronic retention than acute although his reason was perhaps not correct. He said: "When the symptoms come on slowly they are more dangerous than when more urgent and intense at first, because the patient in this case immediately applies to his surgeon for relief."

I have picked out for comment the sections dealing with disorders of the urinary tract, but they occupy only one-fifth of the volume; the rest contains much of great interest in general surgery. Although the description of symptoms is often lengthy it produces a vivid clinical picture of the condition, enlivened by many case histories, and anecdotes. The impression left by the lectures is that Brodie was an accurate observer, a truthful recorder and a first-class teacher. I at least am grateful to his faithful scribe James Taylor of Todmorden Hall for his excellent notes. I am indebted to Mr. J. D. Moys, Town Clerk of Todmorden, for the details of the genealogy of James Taylor.

BIBLIOGRAPHY

BRODIE, B. C. (1832) Lectures on Diseases of the Urinary Organs. London.
—— (1853) Notes on Lithotrity. London.
CIVIALE, J. (1827) Lettres sur la Lithotritie. Paris.
DOUGLAS, J. (1723) Lithotomia Douglassiana; or a New Method of Cutting for the Stone. London.
GREENHOW, E. H. (1879) *Middx. Hosp. Notes*, **2**, 929.
MORRIS, H. (1881) *Trans. clin. Soc. Lond.*, **14**, 31.
PEPYS, S. (1904) The Diary of Samuel Pepys. Edited by H. B. Wheatley. London.
THOMPSON, H. (1879) *Middx. Hosp. Notes*, **1**, 305.

---

## BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

**Dobson (J.), and Wakeley (Sir Cecil P. G.).** Sir George Buckston Browne. pp. 143. Edinburgh and London: Livingstone. 25s. 1957.

**Fasquelle (R.).** Éléments de virologie médicale. pp. 314. Paris: Flammarion. 1958.

**Forrester (G. C.).** The use of chemical tests for alcohol in traffic law enforcement. American Lecture Series No. 50. pp. 91. Springfield, Ill.: Thomas. 15s. 1950.

**Harvey (W.).** The circulation of the blood: two anatomical essays. Translated by K. J. Franklin. pp. 184. Oxford: Blackwell. 22s. 6d. 1958.

**MacKenna (R. M. B.).** Aids to dermatology. 5th ed. pp. 312. London: Baillière, Tindall & Cox. 1956.

**Milcu (St.-M.),** ed. Gusa endemica. Vol. 1. pp. 679. Bucharest: Acad. Repub. Pop. Romine. 1957.

**Reid (D.).** Biology for the citizen. pp. 176. London: Odhams. 1957.

**Shy (G. M.), Bradley (R. B.), and Matthews (W. B., Jr.).** External collimation detection of intracranial neoplasia with unstable nuclides. pp. 144. Edinburgh and London: Livingstone. 30s. 1958.

**Squires (H. C.).** The Sudan Medical Service. pp. 138. London: Heinemann. 15s. 1958.

**United States, Department of Defense.** Emergency war surgery. U.S. Armed Forces issue of NATO handbook. pp. 411. Washington, D.C.: Government Printing Office. $2.25. 1958.

**Wallis (C. J.).** Practical biology for advanced level, medical and intermediate students. Vol. 2, Practical botany. 4th ed. pp. 173. London: Heinemann. 17s. 6d. 1958.

# Section of Odontology

President—G. T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S., L.R.C.P.

[*April* 28, 1958]

## Research, Organization and Teaching in Forensic Odontology

By GÖSTA GUSTAFSON, Dr.odont., F.D.S. R.C.S.Ed.
*Malmö, Sweden*

VERY few people are aware of the forensic aspects of odontology, and few have concerned themselves with the future of this field. It must be admitted that very little research has been done and organization or even facilities for this kind of work are practically non-existent. Furthermore, in only a very few countries is there any teaching in this subject. Such forensic odontology as is practised is usually done *ad hoc* to meet situations, such as accidents or disasters, that suddenly arise. Work done in this way is not to be deprecated but, in my opinion, research, organization and teaching are necessary for the development of efficiency in this field. There is no one in Europe who devotes sufficient time to these matters to be regarded as a scientific worker or specialist in forensic odontology. Those of us who deal with these problems are all amateurs who dabble a little as the occasion arises and then mostly out of personal interest rather than for any material reward.

Although the first great written work on forensic odontology was published some sixty years ago by Amoëdo (1898) of Paris, there are, as far as I know, only two professors in this field in the whole world and both are in Spanish-speaking countries, Cuba and Brazil.

### *Recording in Dental Practice*

The records kept by dentists are usually relatively inadequate. Nevertheless they have sometimes proved of inestimable value as a means of identification.

International standardization of dental recording systems would be a step forward because the need to transmit information of this kind across international frontiers is not uncommon. There is scope for statistical research in this field and the possibility of designing a suitable punch card system could be explored. Furthermore, a central international register of the dental data of all missing persons would very often make the identification of a body a relatively easy matter.

The value of artificial dentures in this respect could be very much enhanced if dentists could be persuaded to mark their own products in accord with some system which would not be very difficult to evolve.

It may in the future be necessary to register regularly the dental data of some special groups of the population. Some military personnel are so selected that they have had very little dental treatment and thus their records made in the usual simple manner would be of little assistance in identification. A more detailed and elaborate system of recording dental data is required in these cases.

### *Recording of Data from Dead Bodies*

In view of the fact that it is impossible to predict what trivial features may prove to be of significance, the recording of the characteristics of the dentition of a corpse should be in great detail and made with meticulous care; for example, not only the position of each filling but its extent, quality of workmanship and the material of which it is composed should be noted. Reliable records of this kind can only be made by a dentist and preferably by one who has had some special experience or training in this work. The recording of the dental data should never be undertaken by the police or by others unfamiliar with the minutiæ of dental anatomy and dental treatment.

### *Identification*

In practice identification is achieved by matching the unknown body with a known missing person and it is difficult for the police to know how to start a search until the possibilities have been narrowed down by knowing something of the characteristics of the unknown person, such as age, sex, the social group to which he belonged or where he lived.

Fortunately, a good forensic odontologist, if this curious word may be used, should be able to say a lot about the dental treatment given. To do so he must have a broad knowledge of how dental treatment is carried out in different countries and by differently trained dentists. It is my experience that treatment in different countries differs a great deal. Recognition of dental treatment of foreign origin may provide a very useful starting point in seeking to identify a body.

One very instructive case reported by Strøm (1946, 1954) in Norway shows the importance

of dental experience. A dead body was found in a shed near Oslo. Near the victim there was a bottle of cheap corn brandy and therefore the police at first thought that the body was that of an ordinary tramp. The dentist who was asked to give an opinion found, however, a number of carefully done fillings in the teeth. It was thus evident that the man had been relatively wealthy and had cared for his teeth regularly. As this occurred during the Occupation it was thought that the person had been in the Resistance movement and the search was made therefore among such people. In due course it turned out beyond question that he had been a rich business man who, together with a friend, intended to fly to Sweden. He was then murdered by his companion who took his money.

Even negative evidence of identity may be of great value. Identity apparently established by clothes, rings and other personal belongings may be proved to be wrong. Loose personal belongings can be stolen, given away or lent. Moreover, they may be deliberately exchanged in order to deceive insurance companies. In all cases where loose belongings are the only evidence of identity the teeth should be used for final identification; unlike clothing, fillings in teeth cannot be transplanted from one individual to another.

For an example of identification aided by dental records I can again refer to Strøm (1956). He describes a flying accident in Norway in which one of the badly burned female bodies was identified as his daughter by a man who recognized the trousers she was wearing. Another body was, however, identified beyond question as that of his daughter on the basis of the correspondence of the dentition with the particularly well-recorded details of dental treatment produced by her dentist. In fact the daughter had loaned her trousers to another girl in the plane.

Nowadays identification with the aid of dental treatment could surpass identification by fingerprints as nearly every citizen has his teeth treated whereas only criminals and visitors to the United States of America have their fingerprints taken.

### *Reliability of Dental Identification*

It has been said that "duplication of two dentitions has never been found." The value of odontological identification, however, as compared with fingerprints, depends entirely upon the experience, accuracy and attention to detail of the original recorder. It is this only which avoids duplication in records of different dentitions.

Special training is needed in charting for accurate identification.

When the records from an unknown body and those from a dentist's records are compared difficulties are again encountered. No data exist concerning the degree of certainty it is possible to obtain from a comparison of dental records. It is clear that doubt may remain even though the data from records correspond with the data taken from a body. This can happen in those cases where very little dental treatment has been given and where the treatment is not out of the ordinary. The fact that the progress of caries tends to follow a common pattern in many mouths increases the likelihood that two persons may show the same type of fillings in the same teeth.

Identification presents fewer difficulties when the names of the victims are known, as in a flying accident. It is merely a problem of organization, at least when the victims are adults of various ages. The difficulties are greater when groups of children have been killed by fire or similar disasters. In Malmö we have made some observations in a school where all children have been treated by the same experienced and skilful dentist, using only two different filling materials, namely silicate and amalgam. We found that in every class of about 30 individuals at least two or three children had identical dental records. It is evident that in the case of disasters affecting children from the same school the usual simple dental records could be of little value. Since children from the same schools so often travel in groups in buses, trains and even aeroplanes this is a problem worthy of effort to devise a more detailed system of dental recording. Photographic records or plaster casts of the mouths, although expensive, are worth consideration.

*Communication.*—I have recently been concerned with the problem of communication of data between different places in cases of flying accidents. The difficulties are particularly great when the two places are situated in different countries with different languages and different systems for describing the dentition. An international telegraphic code has been discussed but no method immune from risk of errors has yet been devised. Quite a lot of time is required to transcribe data into a code and then back again. Furthermore the risk of error is duplicated. It may well be better to use straightforward description in the language of the country transmitting the message and to rely upon accurate translation where necessary.

*Sex differences.*—It is certain that there is a need for methods of determining racial affinities, sex and age. This applies particularly in cases where very little or nothing is known of extensively macerated and dismembered remains. There is, however, no reliable method of determining sex from the dentition.

*Age determination.*—Only a beginning has been made in the assessment of age from the dentition. Much more research is required.

*Bite marks.*—Bite marks on human skin and in inanimate materials present quite different problems. Research should be carried out on the way human skin changes after a bite. The deformations must obviously follow a certain pattern depending on the structures of the tissues and here only a close co-operation between the forensic pathologist and the dentist can give good results.

In bite marks on human skin every tooth cannot be expected to give a definite mark. Only those parts of the teeth which come into contact can be recognized and lateral movements during biting are very common. Therefore it is essential to make impressions of the teeth and to place them into an articulator which enables the teeth to be moved into contact with each other. It is perhaps unnecessary to say that those who deal with human bite marks must be very familiar with bite habits and with the articulation of teeth. Furthermore, since we are all influenced to some extent by what we expect to find I would say that it is advisable when investigating bite marks that two dentists should co-operate, one doing the description of the bite marks and the other the description of the teeth of the suspect, before they are allowed to make comparisons. Bite marks in inanimate materials are in a way much more informative and easier to deal with.

*Time lapse since death.*—The teeth of individuals who have been in water for a certain time change colour and become red-brown. It does not appear to be known how long it takes for these colour changes to occur and it would seem possible that some good would derive from a study of this phenomenon.

*Training of the dentist.*—There is an undoubted need for training a limited number of dentists in this special field, both in its scientific and practical aspects. These would form a nucleus for expansion in time of war. It is essential also that a course in forensic dentistry should form part of the basic undergraduate curriculum.

The identification of the victims from big disasters, particularly fire accidents like the burning of the steamship *Noronic*, needs planning and team work. It is very uncertain whether at short notice enough dentists could be found willing to deal with 400 or 500 badly burned bodies, where only partial remains are available and where recognition by superficial examination is usually out of the question.

There is undoubtedly a need for an accident commission in which medical examiners, police departments and dentists co-operate. It would be advisable to have two dentists working, one in the field investigating the remains and one at home collecting and comparing the investigation with data from dental records.

It is evident that there is growing awareness of the value of dental identification but it is also clear that dentistry cannot fulfil the requirements unless training, research and teaching receives more support from the authorities.

REFERENCES

AMOËDO, O. (1898) L'Art Dentaire en Médecine Légale. Paris.
STROM, F. (1946) *Odont. Tidskr.*, **54**, 443.
—— (1954) *Int. dent. J.*, **4**, 527.
—— (1956) *Norske Tanndlægeforen. Tid.*, **66**, 553.

## The Assessment of Age from the Dentition

By A. E. W. MILES, F.D.S., L.R.C.P., M.R.C.S.
*London*

AGE assessment is one of the most important problems of forensic odontology. It may for example be necessary to try to assess age from a single isolated tooth. During the period of tooth development up to about the age of 20 years it is possible to assess age from the teeth and jaws with a moderately high degree of accuracy, up to the age of 14 years probably with an error of little more than one year. Between 14 and 20 years the accuracy diminishes progressively as more and more reliance has to be placed on one tooth only, namely the third molar which appears to be more variable in its time of development than other teeth.

For the assessment of age during the period of tooth development recourse is made to tables of the chronology of tooth development, the diagrammatic one prepared by Schour and Massler (1941) being the most commonly used. In order to ensure that the data given in this table hold good for English children and to test the accuracy with which age could be assessed by it, the ages of 58 children were estimated from lateral jaw radiographs of the cheek teeth, solely with the aid of the table. Fig. 1 sets out for comparison the real and estimated ages. Up to the age of about 12 years most estimates fall near the real age, few being more than a year out. Over the age of 12 years, however, there is an increasing amount of scatter and many are two years or more above or below the line. Although the

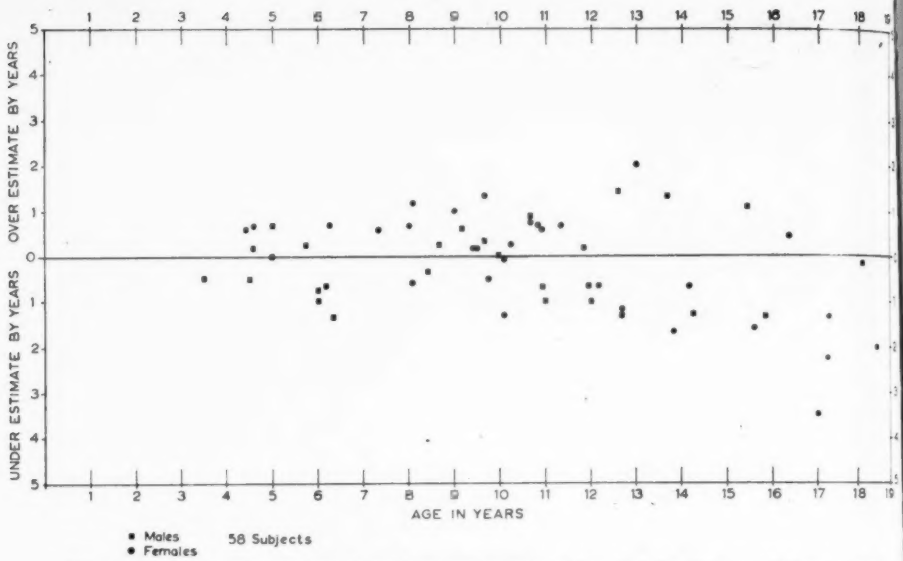



FIG. 1.—Estimates of ages from lateral jaw radiographs of the mandibles of 58 children, using table of chronology of tooth development of Schour and Massler (1941). The horizontal line represents the real ages.

sample is too small for any definite conclusions to be drawn, the fact that the estimates fall about equally above and below the line suggests that the table of Schour and Massler is accurate for English children but that certainly in later childhood there is a considerable range of variation in the chronology of tooth development. It may be significant that the estimates tend to fall consistently too low over the age of 16 years and it is possible that the table needs some correction for the chronology of development of the third molars.

Clements and his colleagues (1953) have provided extremely useful data on the chronology of clinical tooth eruption in English children as opposed to tooth development studied radiographically. The exhaustive study of the chronology of development of the permanent mandibular first molar in American children published by Gleiser and Hunt (1955) is a model of its kind and if extended to other parts of the dentition would be of enormous value for forensic purposes. The collection of corresponding data on English children would be advisable in case racial and environmental factors influence the timing of tooth development more than is suggested by my own very limited investigation.

As an illustration of age assessment during the early phase of tooth development it is appropriate to recount an experience in respect of the mummified remains of an infant found in a trunk. Figs. 2 and 3 show radiographs of the mandible. The symphysis showed signs of commencing closure and tooth development was a little more advanced than at birth; for example, two cusps of the first permanent molar were formed (Fig. 3B). The age was therefore estimated to be 3 or 4 months of post-natal life. Some time later a longitudinal ground section of one of the first molars was prepared and a prominent incremental line in the position of a neonatal line was found in both the enamel and dentine. By measuring the thickness of dentine on the pulp side of this line confirmatory evidence was obtained that our age determination was correct. Massler and Schour (1946) have shown that deciduous dentine is laid down at the approximate rate of 4 $\mu$ per day. The thickness of dentine in the present case was 312 $\mu$ giving an estimate of 3 months and 9 days, allowing 15 days for neonatal arrest of dentine growth.

After the completion of tooth development it becomes increasingly difficult to assess age accurately. This is illustrated by the results of age estimations recently made on 47 skulls of the early part of the last century from a burial ground in the City of London. The real ages were known from data on the coffins but were, of course, unknown to me at the time the estimations were made. In making the estimations account was taken of the teeth and jaws only and other features, such as cranial sutures, were ignored. The results are depicted in Fig. 4. Where the vertical lines cross the circles the real age came within the estimated range and in the three instances where the mid-points of the vertical

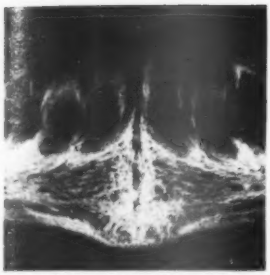


FIG. 2.—Radiograph of mandible of the unknown infant. The lower part of the symphysis is united.

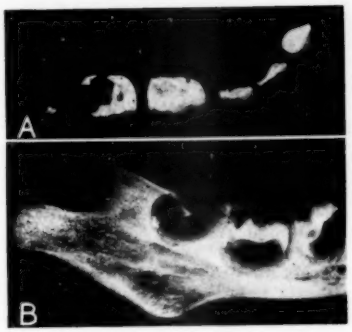



FIG. 3.

FIG. 3.—A, Formed parts of teeth from mandible of newborn infant. The cusps of the second deciduous molar are not fused to form a complete occlusal surface and the tip of one cusp only of the first permanent molar is formed. B, Radiograph of mandible of the unknown infant. Two cusps of the first permanent molar are present.

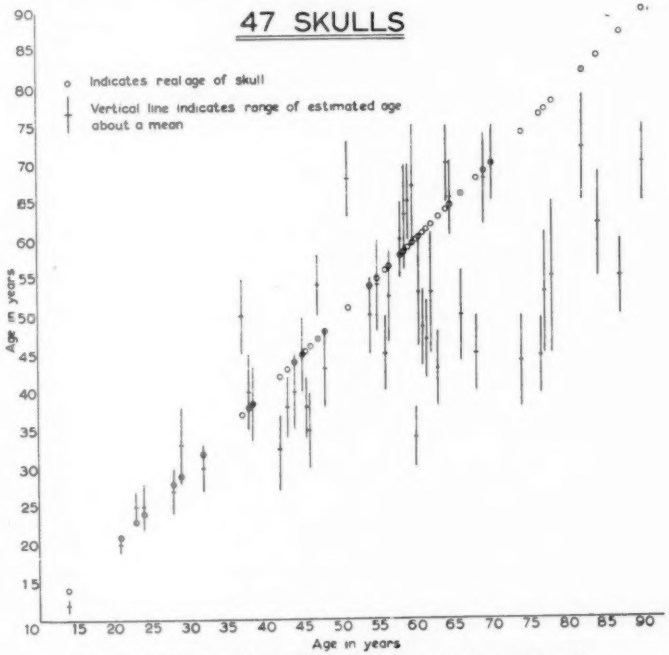



FIG. 4.—Estimates of age of 47 skulls from the jaws and teeth.

lines fall on the circles the estimated age corresponded exactly with the real age. The group below the age of 35 years shows a fairly close score but there is a good deal of scatter between the ages of 40 and 70 years. It is of interest that all the estimations for skulls over the age of 70 years fall well below the real ages. This is no doubt due at least in part to a tendency to discount the chance of there being in any collection of skulls any from persons who have survived beyond the usual span of life.

In mitigation of this rather poor performance it should be noted that no evidence was obtained from radiographs, the degree of closure of cranial sutures, which is admittedly unreliable, or other cranial features.

The age estimations were made by what may be called the intuitive method; that is, by a subjective evaluation of a number of factors, some not easily defined, but which were

principally attrition, the condition of the supporting tissues of the teeth and, where it was possible to remove teeth from their sockets, the thickness of the cementum. Gustafson (1950) has evolved a method which is much more scientific and which at least in his hands would undoubtedly have given a better result. His method makes use of six features which alter with advancing age; attrition, the gingival attachment migrates towards the apex, the size of the pulp cavities diminishes, the translucency of the apex and the thickness of the cementum increase and areas of resorption of the root surfaces increase. With the aid of a longitudinal ground section he allots points to each of these features separately according to degree and finally assesses age by comparing the total points scored with similar data collected from teeth of known age. As no doubt he would agree, the successful use of his method depends upon the observer having a good deal of previous experience. Nevertheless he has made a very substantial contribution to this subject by showing the way to tackle the problem. It is possible that the principle of his method, assigning values independently to as many criteria as possible and then comparing the total values with similar data from material of known age, could with advantage be applied to the degree of closure of cranial sutures.

Scott *et al.* (1949), using replicas of enamel surfaces, found that certain changes in the surface details are consistently related to age. Particularly as these changes appear to be independent of the factors causing occlusal wear (Pedersen and Scott, 1951), they might possibly provide another criterion to be added to the six used by Gustafson. An endeavour to substitute actual measurements for the subjective allocation of points to the criteria might prove fruitful. If this were possible it would enable relatively inexperienced people to make use of data collected by other workers and so help to overcome the difficulty Gustafson has referred to of training people to do this sort of work.

One of the things that makes forensic work so interesting is that it is necessary to examine closely morphological details which otherwise would receive little attention. An example of this which has been reported elsewhere (Miles and Fearnhead, 1953) derives from an attempt to assess the age of a fragmentary maxilla in which the third molar was fully erupted and unmarked by attrition and behind which was a well developed bony tuberosity. It was at first argued that such a tuberosity would not be found until several years after the eruption of the third molar and the age was assessed at about 25 years. The examination of radiographs of a number of subjects aged about 20 years, however, showed that it is quite common for there to be a well developed tuberosity at this age. On this basis and the relatively large size of the pulp cavities in the molars the age estimate was therefore revised to 20 $\pm$ 1 year which proved to be quite close to the otherwise proven real age.

In general the dentition gives very little assistance in the determination of sex and individual teeth have no stigmata of sex at all. The determination of sex from the skeletal remains of sexually immature children is extremely difficult and uncertain, but Hunt and Gleiser (1955) have suggested a method which makes use of the fact that, whereas there is little or no sex difference in the chronology of tooth development, skeletal maturation is about one year earlier in the female than in the male. Hunt and Gleiser determine the age of the skeletal remains from the dentition by using Schour and Massler's tables of tooth development and then the age is determined independently by a study of the maturation pattern of the bones of the hand or some other part of the skeleton making use of data published by Greulich and Pyle (1950). If the dental and bone ages correspond closely the skeleton is probably male and if the bone age is advanced in comparison with the dental age it is probably female. In a blind test of the method Hunt and Gleiser sexed correctly 73% of a sample of 2-year-old children and 81% of 8-year-old children. This technique might well prove of value to those called upon to deal with forensic problems.

*Acknowledgment.*—I am grateful to the Rev. Cyril M. Armitage, M.V.O., M.A., Dr. J. C. Trevor and Dr. F. L. D. Steel for providing access to osteological material exposed during post-war excavations at St. Bride's Church, Fleet Street, London.

## REFERENCES

CLEMENTS, E. M. B., DAVIES-THOMAS, E., and PICKETT, K. G. (1953) *Brit. med. J.*, i, 1421.
GLEISER, I., and HUNT, E. E., JR. (1955) *Amer. J. phys. Anthrop.*, **13**, 253.
GREULICH, W. W., and PYLE, S. I. (1950) Radiographic Atlas of Skeletal Development of the Hand and Wrist. Stanford.
GUSTAFSON, G. (1950) *J. Amer. dent. Ass.*, **41**, 45.
HUNT, E. E., JR., and GLEISER, I. (1955) *Amer. J. phys. Anthrop.*, **13**, 479.
MASSLER, M., and SCHOUR, I. (1946) *J. dent. Res.*, **25**, 145.
MILES, A. E. W., and FEARNHEAD, R. W. (1953) In: Medical and Scientific Investigations in the Christie Case. By F. E. Camps. London; chap. VI.
PEDERSEN, P. O., and SCOTT, D. B. (1951) *Acta odont. scand.*, **9**, 262.
SCHOUR, I., and MASSLER, M. (1941) *J. Amer. dent. Ass.*, **28**, 1153.
SCOTT, D. B., KAPLAN, H., and WYCKOFF, W. G. (1949) *J. dent. Res.*, **28**, 31.

## BOOK REVIEWS

**A Symposium on Non-toxæmic Hypertension in Pregnancy.** Edited by Norman F. Morris, M.D., M.B., B.S., M.R.C.O.G., and J. C. McClure Browne, B.Sc., M.B., B.S., F.R.C.S.Edin., F.R.C.O.G. (Pp. xii+243; illustrated. 35s.) London: J. & A. Churchill Ltd. 1958.

In the summer of 1957 a symposium on non-toxæmic hypertension in pregnancy was held in The Institute of Obstetrics and Gynæcology at Hammersmith Hospital. Contributors included physicians, obstetricians, pædiatricians, pathologists and geneticists. Guest speakers came from Europe, North America and as far away as China. The symposium was arranged in five parts: (1) The maintenance of normal blood pressure and the changes observed in the early stages of hypertension: (2) the course of pregnancy complicated by essential hypertension; (3) the course of pregnancy complicated by other hypertensive disorders (renal lesions, phæochromocytoma, coarctation of the aorta); (4) the management of pregnancy complicated by hypertension; (5) the remote prognosis.

Such was the scope of the conference at which this constellation of experts ranged over every aspect of this disease—one of the major problems in obstetric medicine. In this book will be found the latest information and no clinician, be he physician or obstetrician, can afford not to include this volume in his library.

**Lectures on the Scientific Basis of Medicine.** British Postgraduate Medical Federation. Vol. 6, 1956–57. (Pp. ix+393; illustrated. 45s.) University of London: The Athlone Press. 1958.

These collections of lectures given before the British Postgraduate Medical Federation have amply justified their purpose and are now established as important additions to the bookcases of a wide variety of medical readers.

The sixth volume is no exception. It contains 21 lectures varying in their subject matter from global problems, such as the biological significance of atomic energy and the resistance of staphylococci to antibiotics, to expanding but largely academic subjects, such as problems in connexion with the phospholipids, and the synthesis and degradation of the polysaccharides, and to more clinical matters, including the role of the endocrine system in breast cancer and the causes of pain.

This volume will enhance the reputation of the series.

**Studies on Fertility 1957.** Vol. IX of Proceedings of the Society for the Study of Fertility. Ed.: R. G. Harrison, M.A., D.M. (Pp. x + 169; illustrated. 25s.) Oxford: Blackwell Scientific Publications. 1958.

This ninth annual volume on fertility ranges far and wide from animal experiments to gynæcology. The first Oliver Bird Lecture (by T. Mann, on the Biochemical Basis of Spermicidal Activity) is included. This important paper covers the effects of enzymic inhibitors, detergents, &c., and foreshadows the possibility of effective parenteral administration. Work by Jones and Harrison on mice points to the cause of the infertility so frequently associated with human pathological obesity. The second half of the book is devoted to the female, human and animal. The first chapter is critical of the therapeutic value of tubal patency tests. There follows an important paper on genital tuberculosis, stressing the necessity for early diagnosis and treatment and emphasizing those symptoms and signs which should be regarded as justifying immediate treatment—especially those kymographic and radiological pointers which often precede endometrial proof by several vital months. The volume concludes with more animal experiments, but if those on ovarian grafts are eventually applied to human infertility they will cause even more controversy than A.I.D.

**Essentials of Fluid Balance.** By D. A. K. Black, M.D., F.R.C.P. (Pp. xiv+127; illustrated. 15s. 6d.) Oxford: Blackwell Scientific Publications. 1957.

Black's book differs in approach from the majority of the books dealing with fluid and electrolytes and, in the reviewer's opinion, is one of the most readable.

It is short, but in its 127 pages there are excellent summaries of the present views on

regulation of body fluid, on sodium and potassium metabolism and on acid base balance. Water and electrolytes and their mutual interrelations are subjects which always cause some worry at first to the non-specialist, and to cover the whole subject in this limited space means that the work is highly concentrated, and has to be studied carefully: nevertheless all the chapters are very well put together and the whole book is a pleasure to read.

It does not, like so many of the present books, claim to be a practical guide to salt and water therapy: in fact only 14 pages are specifically allocated to therapy, but the physician, surgeon or pathologist who has digested the five previous chapters will be in a very good position to begin to plan his fluid therapy on a rational basis. It is certainly very strongly to be recommended as an introduction to any doctor who is in any way concerned with fluid balance.

**A Manual of Stomatology for Dental and Medical Practitioners.** By J. P. Walsh, M.B. Foreword by Sir Charles Hercus. (Pp. 130; illustrated. 30s.) Christchurch, N.Z.: N. M. Peryer, Ltd. London: Lloyd-Luke, Ltd. 1957.

Much personal clinical experience has been recorded in this small volume, which constantly stresses the value of co-operation between the medical and dental professions. The book is based on lectures given to fifth year medical students. Twenty pages are devoted to embryology, anatomy, histology and physiology which might be considered pre-clinical subjects, but their inclusion in the book makes the survey more complete. The few illustrations are clear and useful and the text is enlivened with well-chosen short case histories. The dental student might find the book useful in revision while the medical student will gain from it a useful insight into dental disease. Both will wish that other "manuals" might be of similar size.

**The Kidney.** By H. E. de Wardener, M.B.E., M.D., F.R.C.P. (Pp. viii + 338; illustrated. 45s.) London: J. & A. Churchill, Ltd. 1958.

This book has been written for medical students but it will appeal to those undertaking post-graduate studies. The text is based on the physiology and anatomy of the kidney, both aspects being adequately summarized in the first eight chapters. The remainder of the book is devoted to renal disease, and Dr. de Wardener introduces a classification based more on functional than anatomical changes. By doing so the treatment of disorders of renal function becomes more logical, and in many instances is self-explanatory. He also introduces his own impressions which are obviously based on an intimate knowledge of the subject.

Naturally, in dealing with such a controversial subject, disagreement with some of the statements is to be expected. For instance, is it really necessary "to catheterize the bladder to exclude urinary retention" (p. 115) and to place an indwelling catheter in the bladder in acute renal failure (p. 117)? The urologist, in his quest for yet smaller parathyroid tumours, would certainly question that the diagnosis of hyperparathyroidism is dependent on the findings of a low plasma phosphate (p. 157).

These and other discrepancies, however, are but minor points for the excellence of the presentation compels us to recommend the book. We hope that Dr. de Wardener will continue his work for we are sure that the second edition will be as popular as the first.

**Leptospirosis in Man and Animals.** By J. M. Alston, M.D., F.R.C.P.Ed., and J. C. Broom, O.B.E., M.D. (Pp. xii + 367; illustrated. 40s.) Edinburgh and London: E. & S. Livingstone, Ltd. 1958.

There has been a great increase in knowledge of leptospiral infections both in man and in animals during the forty-one years which have elapsed since the ætiology of Weil's disease in man was established.

A mass of information concerning the causal organisms and their classification, reservoir hosts, epidemiology, incidence, pathology, clinical aspects, diagnosis and treatment has been marshalled and presented in a masterly fashion in the book under review.

Laboratory workers, public health officers, medical practitioners and veterinary surgeons will all find it a reliable source of information. Two features of special interest are the excellent table showing the serological relationships between 39 different strains and a very interesting section written by a barrister on the legal aspects, in England and Wales, of occupational infections.

The illustrations have been well chosen and there is an excellent bibliography. The print is very clear and the book pleasant to handle and to use. It can be recommended with confidence.

# Section of Medicine

President—A. H. Douthwaite, M.D., F.R.C.P.

[*October* 28, 1958]

## The Development of the Treatment of Duodenal Ulcer [*Abridged*]

### PRESIDENT'S ADDRESS

By A. H. Douthwaite, M.D., F.R.C.P.

The natural division of treatment into diet, sedation, antispasmodics, and antacids still obtains, as it did in the early 1920s, but the relative importance of one to the other has altered in the last few years.

#### Diet

The monotonous diet which was then employed consisted of the giving of milk every two hours in quantities of about three to four ounces, water, glucose, and lightly boiled egg. This depressing regime was maintained until occult blood had disappeared from the stools. It is noteworthy that this frequently did not take place in less than four weeks in spite of the fact that the patient was lying in bed. The more adventurous physicians might add pounded fish, thin bread and butter, custard and fruit juice when the patient had lost his pain. In about a month he was allowed cold boiled bacon as a tribute to fat's depressant action on gastric secretion. Breast of chicken might come in the fifth or sixth week. It may well be that the nauseating effect of such a diet produced inhibition of gastric secretion and thus helped healing. Although there was no doubt that the administration of milk caused rapid relief of pain Ryle noted that it caused a considerably higher acidity than did water.

Later Meulengracht published his observations on the generous administration of food, including minced meat, to those who had hæmatemesis and, although many will not entirely approve of his scheme, there is no doubt that his observations shook the complacency of the physician and from that time onwards a rapid improvement and much greater generosity in diet resulted. So unsatisfactory were the results up to that time that it was regarded as axiomatic that patients who relapsed after six weeks' full medical treatment should be subjected to gastrojejunostomy. Although in many parts of the country we still meet with patients who are treated for long periods with milk and milky foods, the accepted attitude now is that virtually all food may be taken provided that it is chewed thoroughly before being swallowed. Chemical irritants such as mustard, alcohol, spices and vinegar should be avoided, as also should fried foods. There is certainly no clinical evidence that the administration of meat does harm although there may be theoretical objections to it, neither can there be any reason, once the ulcer has healed, for forbidding wine with food in moderation, but the taking of strong alcohol such as cocktails on an empty stomach is clearly unwise. Alcohol acts centrally by stimulating secretion, and possibly by the release of gastrin.

#### Sedation

The possible importance of anxiety as a cause of duodenal ulceration and as a factor in its persistence, though hinted at occasionally from the early part of this century, rose to

prominence shortly after the 1914–18 War. The development of the first symptoms a week or two after an episode of extreme anxiety, or again relapse arising at times of mental stress, and the remarkable freedom from trouble during holiday periods all seemed to support the view that the mental state, mediated through the vagi, might indeed be of the utmost importance. The later classical work of Wolf and Wolff (1943) in their observations on Tom with a gastric fistula showed the remarkable changes which could occur in the mucosa of the stomach under the influence of mental perturbation. Treatment by psychiatrists did not give very satisfactory results and the same depressing sequence of ulceration, rest in bed, recovery and then relapse two or three times a year was unaffected by the new approach. The use of phenobarbitone, however, to relieve anxiety became widespread and from 1925 onwards for twenty years it was rare to meet a sufferer from duodenal ulcer who was not taking it. It must be remembered that in the period between the two great wars, anxiety was a potent factor in the hospital patient. There was no full employment and a week or two of sickness might readily lead to the loss of a job, and recurrent sickness almost invariably did so. Extreme poverty stared these people in the face and obviously neither psychotherapy nor phenobarbitone could be an effective barrier between the mind and the stomach. Furthermore, the misery and depression resulting from this grim economic outlook might in fact be increased by phenobarbitone; certainly no form of barbiturate has ever produced the euphoria which one would wish for. It was this consideration which led to the use of cannabis (Douthwaite, 1947), a drug which in the majority produces a sensation of extreme pleasure, remarkably good appetite, and no constipation. It must be admitted, however, that it is capricious. The visions which it produces are not always pleasant and sometimes acute fear is engendered by the drug, especially in women. Used therapeutically it is a drug of very feeble addiction: this aspect has been grossly overstressed by those whose only knowledge of it is in relation to the moronic underworld of the United States. Two factors, however, have rendered the regular use of sedatives no longer necessary. They are the enormous improvement in the economic position of the working classes, and the development of an understanding of parasympatholytic drugs which can protect the stomach from cerebral influence. There is from time to time an indication for the use of sedation in the daytime and of course at night to secure sleep, but it should no longer be routine. The matter, then, of diet and sedation has now sunk to one of minor importance and the treatment of duodenal ulcer has thus been simplified.

### Antispasmodics

The parasympatholytic drugs which make up this group had as their starting point the alkaloids of belladonna, notably atropine which had been observed to reduce the output of gastric juice in experimental animals. As far back as 1918 Crohn referred to the transient and poor effects of atropine on gastric acidity. Belladonna was made popular in the treatment of duodenal ulceration by Bennett (1922). Ryle (1923) writing on the treatment of duodenal ulceration advised the administration of 5 minims (0·3 ml.) of tincture of belladonna before alternate two-hourly feeds and 1/100 grain (0·65 mg.) of atropine hypodermically every night. He believed that the relaxation of the pylorus produced by atropine encouraged a reflux of bile into the stomach and that it was this which reduced acidity. The conviction that this dosage of belladonna alkaloids appreciably affected gastric secretion held sway unchallenged until 1938 when Davidson and Nicol communicated to a meeting of the Gastroenterological Club, as it then was, the results of their researches which showed that even toxic doses of atropine had no constant or marked influence on gastric acidity. Nicol (1939) reiterated that atropine often failed to influence gastric secretion and that its value lay in antispasmodic effect. Although the original iconoclastic pronouncement was received with frigid incredulity by the gastroenterologists it was not long before full confirmation was available, and one of the great props to the treatment of duodenal ulcer appeared to have been knocked from under our feet. It is true that current dosage was too low, but there is no doubt that even toxic amounts are unreliable. Yet adequate doses of belladonna or its alkaloids will relieve pain in most patients. If this is not due to reduction in the concentration of acid in the gastric juice, to what can it be attributed? From observations on the total gastric juice output, as opposed to its pH, it has been established that these drugs do reduce it appreciably. Thus food or antacids, both of which temporarily reduce the gastric acidity, will have a smaller volume to combat and therefore their efficacy will be improved.

For many years there was a sharp difference of opinion as to the pain-producing factor in duodenal ulceration; one school which favoured muscular contraction and increased tonus was led by Bolton (1928), Christensen (1931), Hurst (1911), Ryle (1926), and Poulton (1928), and myself (Douthwaite, 1947). It must be admitted that pain cannot always be

overcome by antispasmodics, and even such powerful drugs as hexamethonium may fail to influence it. It may well be that we have a double factor at work, but I have no doubt that the supporters of the acid theory are right that it is the most important cause of pain and the tendency to relapse. This school originally based on Palmer's work (1926) obtained heavy support from the outstanding clinical work of Bonney and Pickering (1946). Hyoscyamine became the drug of choice in 1947 for use in conjunction with antacids to encourage a reduction in the rate of emptying of the stomach and thus prolongation of antacid effect. It was particularly valuable given at night with a large dose of alkali. The advent of hexamethonium, and its effect in causing cessation of gastric and intestinal movement, soon led to its use to secure rest of the gastro-intestinal tract. Its many unpleasant side-effects including postural hypotension, and the difficulty in obtaining the desired degree of gastric immobility, as opposed to dangerous ileus, prevented its becoming a drug of regular use, but injected intramuscularly at night it could be shown to have a much longer effect than a full dose of hyoscyamine. If administered half an hour before a full dose of alkali and olive oil, protection against high gastric acidity might be achieved for four or five hours during sleep. Aylett and Douthwaite (1955) described the action of tricyclamol chloride (Lergine) on gastric and duodenal motility and tone. They showed it to be a parasympatholytic of remarkable power on the duodenum and jejunum. In several patients it was noted that under its influence the pain of duodenal ulcer disappeared, yet the level of free acid and its concentration was little if at all affected. Given with an alkaline mixture it potentiated it considerably, due no doubt to the retention of the mixture in the stomach. It gradually ousted hexamethonium in the attempt to control nocturnal secretion. The dose is 100 mg. by mouth in combination with aluminium hydroxide gel (10 ml.) given half an hour afterwards. This will usually maintain the pH of the gastric juice at or above 4 for some three hours and thus provide protection for about half the sleeping period. Symptomatically it is effective and the nocturnal pain which is the curse of so many of the sufferers will disappear.

## Antacids

That the presence of acid is important in the prevention of healing of a peptic ulcer is accepted by all and has been recognized for many years. Action of pepsin may be disregarded from the therapeutic angle because it depends upon an acid medium and, therefore, control of acidity will obviously abolish it. Supporting evidence that acidity is important in peptic ulceration is provided by the fact that up to the age of puberty the gastric acidity is the same in either sex and so is the prevalence of peptic ulcer. After puberty the acidity is higher in the male and so is the occurrence of peptic ulcer. During pregnancy there is a tendency for a fall of gastric acidity, and peptic ulcer in women tends to heal during this state.

Admittedly this may be due to other factors. However, again it is noticed that recurrence follows soon after delivery when gastric acidity once again returns to the pre-pregnancy level. Peptic ulcer does not occur when there is a condition of achylia as in pernicious anæmia. X-ray of the stomach in suitable doses can abolish temporarily the secretion of acid and over that period the ulcers heal, but recur when the acid returns. Finally the patient with duodenal ulcer secretes a large amount of acid. Although the output of acid is partly directed by nervous impulses mediated through the vagus, and partly by a hormonal mechanism due to gastrin, the final mechanism of output must depend upon the response of the oxyntic cells of the stomach. For years it was assumed that the high output of acid both by day and by night in patients with duodenal ulcer was due to a combination of nervous and hormonal impulses and it was only comparatively recently that the possibility of the presence of an increased number of secreting cells was envisaged. The work of Hunt and Kay (1954) is very interesting here. They demonstrated that the patient with duodenal ulcer does in fact possess appreciably more oxyntic cells than the normal healthy individual. They used large doses of histamine to produce a maximal secretory response, which is independent of nervous or hormonal influence. In order to do so it was necessary to suppress the unpleasant side-effects. This was rendered possible by the use of an antihistamine drug, so that a patient can be subjected to such a dose of histamine that full response of the stomach secretion will occur and any increase in that dose will not augment secretion further.

By this method it was shown that in persons with duodenal ulcer the increased maximal secretory capacity is in the order of 70% greater than the normal, a finding which receives histological support by Cox (1952) who showed that in male patients with duodenal ulcer approximately 75% more parietal cells were present in the gastric mucosa than in normal individuals. Hunt and Kay raised the question of whether this excess of cells was present from birth or whether it is induced by nervous and hormonal factors. The answer to this

is not yet known but it seems probable that a work hyperplasia occurs for when duodenal stenosis arises from duodenal ulcer there is increased work thrown on the stomach and the maximal secretory capacity is augmented.

If we are agreed that effective antacid treatment is of the utmost importance we must consider the optimal level of acid. It is known that when it is reduced to pH 4 pepsin loses about 80% of its power. We should aim at this figure of 4 therefore. Whether a considerable degree of alkalinity is harmful or not it is difficult to say, although presumably alkalinity greater than that of plasma should be avoided. Probably it is perfectly satisfactory if we work to pH limits of 3·5 to 7.

The traditional methods of administering antacids such as carbonates, triphosphates, trisilicates, or aluminium hydroxide have the outstanding weakness of the intermittent character of the administration. It is impracticable for them to be given more than six times a day. Often they are given three times a day after meals. In 1939, in conjunction with E. B. French, I showed (Douthwaite, 1939) that large doses of antacids depressed gastric acidity for a matter of quarter to half an hour. It is obvious that this must be so because the stomach often ejects its contents with speed, and it is not at all unusual for a meal to be evacuated from the stomach in half an hour. It was this fact which led to the increasing use of alkaline milk drip. In patients lying in bed there is no particular difficulty in arranging for it and the tube can be tolerated well for a matter of a few days. Perhaps its main value was that it could maintain some degree of neutralization of the stomach acid throughout the night. However, this was no answer to the problem of home treatment or indeed to that of the prevention of recurrence. It was with this in mind that I searched for some tablet which could be held in the mouth and allowed to dissolve slowly, and yet which would deliver sufficient antacid to maintain the gastric acidity at an optimal level. It was as it were an attempt to find a substitute for alkaline milk drip which could be used by the patient without difficulty. The upshot of it was the development of tablets, now known as Nulacin, which contain as a basis the solids of whole milk and as antacids magnesium trisilicate (0·25 gram), magnesium oxide (0·12 gram), calcium carbonate (0·12 gram), and magnesium carbonate (0·03 gram). Douthwaite and Batty Shaw (1952) carried out a large number of experiments with these tablets held in the mouth during test meal observations over several hours. The analyses were carried out by my colleague Dr. J. N. Hunt, who reported that the neutralizing power was largely due to the magnesium oxide component.

By good fortune the tablet was made for us with just the right consistency. It did not dissolve too rapidly and it was found that two or at the outside three tablets an hour would exert satisfactory control, sometimes in fact producing a pH as high as 9, but usually a figure of 5 to 7. This encouraging result led to further tests on patients taking ordinary meals, whereas in the first series they were having a relatively non-stimulating meal such as gruel. Douthwaite and Thorne (1954) reported that the antacid effect of Nulacin tablets on 12 patients taking a mixed diet was satisfactory, giving a pH in the region of 3 to 4 and on no occasion one of higher than 6 as compared with the readings recorded on the gruel meals. Control experiments with dummy tablets showed no effect. Control tests eliminated saliva as an important influence.

This new method of the administration of antacids has revolutionized the treatment of duodenal ulcer and has further simplified the matter, for milk drip is no longer part of our therapeutic stock in trade. In some individuals the magnesium produces diarrhœa, although the tablet was designed in the hope of avoiding constipation or diarrhœa. In individuals with faulty renal function and especially those who take an excessive amount of tablets—15 or 16 a day should be the maximum—symptoms of alkalosis have been reported but only rarely.

A search for a buffering agent which could not produce excessive alkalinity of the gastric contents led to the formation of a tablet containing aluminium glycinate (Douthwaite, 1954). The aluminium hydroxide is combined with the amino acid glycine and will give rise to immediate and prolonged buffering. Glycine buffers at a low pH up to 2: a concentration of pH 1 to 2 is common in duodenal ulceration and pH higher than this is controlled by the aluminium hydroxide component. Tablets now known as Prodexin consist of 0·9 gram of aluminium glycinate and 0·1 gram of magnesium carbonate. Fractional test meals again showed control of gastric acidity. Whereas with Nulacin the total and free acid fall together, with aluminium glycinate the free acid falls to zero while the total acid may climb. Thus the acid is held inert until it passes into the intestines. There is of course no danger of alkalosis. Tested on patients taking ordinary food Prodexin raises the pH of the gastric contents to 4 (Clark and Hunt, 1958), and danger of alkalosis does not exist. Further work has shown that four tablets sucked an hour reduces the acidity of the gastric contents to a pH of 4 and in many this is achieved by the sucking of three tablets an ho

We have thus two highly effective preparations which can be used according to taste or indeed in order to vary the taste for the patient who may weary of one flavour from week to week. The Prodexin tablet tends to be slightly constipating. The effect on the bowels of one or other tablet would be an indicator of the best for the individual.

It is so easy to heal an ulcer by almost any means that we should not assess our therapeutic efforts on this phase but rather on our prevention of relapses.

*Relapse.*—In the five years since beginning the use of antacid slowly-dissolving tablets encouraging results have been forthcoming. Of 38 patients with proved chronic duodenal ulcer who had never less than two relapses a year prior to the beginning of Nulacin or Prodexin treatment, at the end of five years 21 have been completely free from relapse, 5 have had from one relapse in two years to one relapse a year, the others have relapsed as frequently as before, or have come to surgery. In all those failures except for 2 who developed duodenal stenosis, the patients admitted to having discontinued the sucking of tablets and of all other precautions within three months of having lost their symptoms. These figures although not giving rise to complacency are very much better than the somewhat smaller list based on the earlier traditional treatment, when of 27 patients with the same relapse rate not a single one escaped further relapse during a five-year period.

*Ion exchange resin.*—Although in theory this would be a most excellent method of dealing with gastric acidity, in point of fact if the tablets are swallowed they are fairly rapidly ejected from the stomach and the same objection therefore applies as to the intermittent administration of alkali. Furthermore if taken in powdered form the taste is most unpleasant.

*Suppression of gastric HCl at source.*—It will be agreed that if a drug could be found which could directly inhibit the oxyntic cells then the ideal antacid would have been discovered and the treatment of duodenal ulcer solved. Janowitz (1958) reported on the remarkable effect of intravenous acetazolamide (Diamox) causing a profound fall in the rate of secretion of hydrochloric acid ranging between 70 and 97% and persisting for three to six hours. This action is due to the inhibition of gastric carbonic anhydrase which is necessary to the secretion of gastric acid. His work points the way to further research, although the use of acetazolamide intravenously is not a practical proposition. The study of the inhibition of gastric secretion by mersalyl (Douthwaite and Booth, 1956) arising from work by Bond and Hunt (1956) showed that mersalyl (0·1 gram in 250 ml. of 12% glucose) introduced into the stomach would arrest the secretion of acid for some two and a half hours, probably as the result of a combination of mercury with the sulphyryl groups of a compound which participates in the acid secreting mechanism. Further work, however, by Booth (1958) showed that although this was a promising development, the drug could not be used with safety because inorganic mercury is liberated when mersalyl is given in this way. In experimental animals mercurial poisoning could be thus produced. I believe that our future success lies in finding a safe substance which inhibits the normal mechanism of secretion by direct action on the gastric mucosa and I point to this as an obvious line of research.

*Twenty-four-hour control.*—Control of daytime secretion is now within our grasp and offers no practical difficulties. At night the sucking of tablets is excluded and we are forced to the use of powerful parasympatholytic drugs to delay the gastric emptying and a large dose of some suitable antacid in the hope that at least two or three hours of the nocturnal secretion will be controlled. A further advance has recently been made in this connexion by the employment of (1–methyl–2–pyrrolidyl) methyl benzilate methyl-methosulphate (Nacton). This drug has parasympatholytic properties somewhat similar to those of atropine. It is worthy of special mention, however, because it is peculiar in its action, there being a lag of several hours before it exerts any activity and indeed it may be several days before the full effect can be determined. Furthermore it has been found (Douthwaite and Hunt, 1958) that its action extends over at least six hours after a single dose and it reduces the total output of gastric HCl by about 60%. Given in quantity necessary to achieve this the side-effects produced by larger doses can be avoided. In this way it differs strikingly from atropine. Furthermore the alkaline non-parietal secretions of the gastric mucosa which have a protective action are not reduced by Nacton. The reduction of acid volume by the drug makes it much easier to obtain more prolonged influence from alkali administration as a single night-dose or as slowly dissolving tablets in the daytime. It should be given at six-hourly intervals, the total initial daily dose being not more than 10 mg. and then increased at four-day intervals from 2 mg. six-hourly to 3, 4 and 5 mg. six-hourly, and

so on until some side-effects are observed. The dose should then be reduced one step, as it were, and this will still give satisfactory control.


## Summary

The treatment of patients with duodenal ulcer now consists of bed-rest for two weeks. During this time a generous diet devoid of obvious irritants, Nacton six-hourly and Prodexin or Nulacin one tablet an hour are given. When the patient is ambulant the same dietetic and medicinal scheme should be maintained indefinitely to prevent relapse, except during restful holidays when the drugs may be discontinued. With acid control established, wine, smoking after meals and late nights are permissible.


## REFERENCES


Aylett, P., and Douthwaite, A. H. (1955) *Brit. med. J.*, i, 691.
Bennett, T. I. (1922) *Lancet*, ii, 866.
Bolton, C. (1928) *Lancet*, i, 1159.
Bond, A. M., and Hunt, J. N. (1956) *J. Physiol.*, **133**, 317.
Bonney, G. L. W., and Pickering, G. W. (1946) *Clin. Sci.*, **6**, 63.
Booth, M. (1958) Ph.D. Thesis. London.
Christensen, O. (1931) *Acta med. scand.*, suppl. 37.
Clark, T., and Hunt, J. N. (1958) *Practitioner*, **180**, 334.
Cox, A. J. (1952) *Arch. Path., Chicago*, **54**, 407.
Douthwaite, A. H. (1939) *Practitioner*, **143**, 461.
—— (1947) *Brit. med. J.*, ii, 43.
—— (1954) *Practitioner*, **173**, 46.
——, and Batty Shaw, A. (1952) *Brit. med. J.*, ii, 180.
——, and Booth, M. (1956) *Gastroenterologia*, **86**, 381.
——, and Hunt, J. N. (1958) *Brit. med. J.*, i, 1030.
——, and Thorne, M. G. (1954) *Brit. med. J.*, i, 183.
Hunt, J. N., and Kay, A. W. (1954) *Brit. med. J.*, ii, 1444.
Hurst, A. F. (1911) The Sensibility of the Alimentary Tract. London.
Janowitz, H. D. (1958) *Lancet*, i, 1353.
Nicol, B. M. (1939) *Lancet*, ii, 881.
Palmer, W. L. (1926) *Arch. intern. Med.*, **38**, 603, 694.
Poulton, E. P. (1928) *Lancet*, ii, 1223.
Ryle, J. A. (1923) *Lancet*, ii, 843.
—— (1926) Gastric Function in Health and Disease. London.
Wolf, S., and Wolff, H. G (1943) Human Gastric Function. London.

# United Services Section

President—Air Marshal Sir HAROLD WHITTINGHAM, K.C.B., K.B.E., F.R.C.P.

[*October* 2, 1958]

## A Review of Hæmodialysis in Renal Failure and Some Points in the Diagnosis of Acute Renal Failure

By A. M. JOEKES, M.R.C.P.
*London*

THE present group of papers discusses some of the results obtained in the Renal Unit at the Princess Mary's Hospital, Halton. This unit has been built up during the last two years as a centre for the treatment of acute renal failure. At first, conservative metabolic treatment was exclusively used but in the last year blood dialysis with an artificial kidney has been available when deemed necessary. Inevitably, the great majority of patients treated have been civilian.

Before the 1939–1945 World War the recognition of acute renal failure with a recoverable renal lesion received no attention. The immense interest in recoverable acute renal failure since 1945 was based on the observations on civilians rather than military casualties. It was the aerial bombardment of London that resulted in a large number of patients with crushing and other injuries dying with acute renal failure. The now classical observations by Bywaters and Beall (1941) laid the emphasis on hæmoglobin pigments in the ætiology of tubular damage giving rise to the renal failure. The histological description of the post-mortem findings was originally made by Shaw Dunn *et al.* (1941) and confirmed by Dible and Bywaters (1942). The prognosis of such patients with renal failure following crushing injuries was extremely grave. I still remember a boy of 19 brought into hospital in 1941 with a moderately severe bruising injury of one leg, which seem to be improving very well, but on the fifth day it was noted that he was passing little urine and the blood urea was found to exceed 200 mg.%; although visited by those working on the problem and with first-class physicians at his bedside, it was considered that he had no chance of recovery and that no known treatment would be of avail. He died on the eighth day after the injury.

By the time of the Allied landings in Italy and France, the picture of acute renal failure complicating severe trauma was well recognized, although no positive therapeutic management had been developed. Lucke's (1946) review of all published cases of acute renal failure, amounting to some 600 cases in all, showed an overall mortality of 90%. In Korea the fatality rate of patients with acute renal failure was 80 to 90% before it was accepted that this complication of severe trauma required expert handling by a specialized unit. In 1952 a Renal Insufficiency Unit was set up, at first without dialysis facilities and subsequently an artificial kidney was used. Of 51 patients admitted to the unit, all severely wounded with acute renal failure, 27 patients survived, a recovery rate of 53% (Teschan *et al.*, 1955).

It is impossible here to give a detailed review of the development in treatment of acute renal failure which made possible the very much better results in the specialized unit towards the end of the Korean war, compared with those obtained, both in battle casualties and civilian patients with trauma or complicating infection, up to 1946. On the one hand, the technique of dialysis—extracorporeal blood dialysis, peritoneal dialysis, gastro-intestinal dialysis, as well as exchange transfusion—aimed mainly at the removal of waste products although electrolyte corrections were also achieved. In this field, Kolff in Holland, with his first publication in 1943, was the great pioneer; in a small provincial town in Holland during the German occupation, he built and used the first artificial kidney. On the other hand there was the development of careful metabolic management of the patients preventing

the development of severe disturbances and so enabling patients to survive sufficiently long for their kidneys to recover. Lattimer (1945), in the U.S.A., first critically analysed the relationship of fluid intake to survival. Kugel (1947) suggested that the basic requirement during the anuric phase was 700 ml. during the twenty-four hours; unfortunately he advocated that this should be given as normal saline which would be equivalent to 100 m Eq. of sodium per day. Borst, in Amsterdam, in 1948 laid stress on the importance of reducing protein catabolism in the uræmic patient. In this country, at Hammersmith Hospital, we (Bywaters and Joekes, 1948; Joekes and Bull, 1948) were fortunate in being given one of Kolff's four original artificial kidneys in 1946. Although dialysing on 25 occasions, we became impressed with the importance of simple metabolic management, maintaining very strict control of fluid intake, attempting to keep protein breakdown to a minimum, with a high calorie, non-protein, electrolyte-free mixture of fat and glucose (Bull *et al.*, 1949). Although fundamentally these principles were right, quantitatively both the water intake and the total calorie requirements have been modified. In essence, the conservative management during the anuric or oliguric phase is now the administration of 600–700 ml. water and from 100–400 grams glucose in twenty-four hours.

The several different types of artificial kidney can be grouped into two kinds:

(1) Those in which the blood inside the cellophane tubing is not under pressure, for example, the original Kolff rotating drum kidney; and (2) those in which the blood in the cellophane tubing is under positive pressure, e.g. Alwall kidney, Skeggs-Leonard and the Kolff disposable coil kidney. Without going into the dialysing properties of the various kinds of kidneys, the striking difference between the two groups is that in the second group, in which the blood inside the tubing is under pressure, water can be ultrafiltered from the blood into the dialysing tube. In the original rotating drum kidney, water could be extracted by making the dialysing fluid markedly hypertonic. This kidney has, however, the very great disadvantage that it is extremely difficult to control, or maintain constant, the amount of blood inside the dialysing tubing.

Although the basis of the treatment of acute renal failure is the day-to-day metabolic management, there can be no doubt that any unit specializing in the treatment of this kind of case should have available the technique of blood dialysis. The two clear indications for dialysis are a high serum potassium not responsive to other forms of treatment, and marked overhydration; the latter indication is probably a strong argument for using the second type of artificial kidney. At Halton, the Kolff disposable type of kidney is in this group.

*Diagnosis*

The prognosis of patients with acute reversible renal failure is very much improved by correct management in the early stages. Such management will only be instituted if the diagnosis is made early after the onset of kidney damage.

In any situation where renal failure may occur—following hæmorrhage, "shock", dehydration, after major operations, abortion, ingestion of various poisons, &c.—the very simple precaution of *total* twenty-four-hour urine collection should never be omitted.

Once renal failure is established, an ætiological diagnosis must be attempted. If there is no history of an episode that could explain the onset of acute tubular necrosis or cortical necrosis, various investigations may be helpful, or the history and examination of the urine may have suggested a glomerular nephritis.

An ætiological diagnosis is essential for prognosis. In prolonged oliguric renal failure it is important to know whether the renal lesion is recoverable. Renal biopsy may be of considerable help as a guide to whether a patient should be maintained in life as long as technically possible with repeated dialysis.

REFERENCES

BORST, J. G. G. (1948) *Lancet*, i, 824.
BULL, G. M., JOEKES, A. M., and LOWE, K. G. (1949) *Lancet*, ii, 229.
BYWATERS, E. G. L., and BEALL, D. (1941) *Brit. med. J.*, i, 427.
——, and DIBLE, J. H. (1942) *J. Path. Bact.*, **54**, 111.
——, and JOEKES, A. M. (1948) *Proc. R. Soc. Med.*, **41**, 420.
DUNN, J. S., GILLESPIE, M., and NIVEN, J. S. F. (1941) *Lancet*, ii, 549.
JOEKES, A. M., and BULL, G. M. (1948) *Proc. R. Soc. Med.*, **41**, 678.
KOLFF, W. J., and BERK, H. T. J. (1943) *Ned. Tijdschr. Geneesk.*, **87**, 1684.
KUGEL, V. H. (1947) *Amer. J. Med.*, **3**, 188.
LATTIMER, J. K. L. (1945) *J. Urol.*, **54**, 312.
LUCKE, B. (1946) *Milit. Surg.*, **99**, 371.
TESCHAN, P. E., *et al.* (1955) *Amer. J. Med.*, **18**, 187.

A paper on **Biochemical Aspects of Hæmodialysis** was read by Dr. J. E. SCOTT (Halton).

# Experiences with the Kolff Twin Coil Artificial Kidney at the Renal Unit, Princess Mary's Royal Air Force Hospital, Halton

By Group Captain R. C. JACKSON, M.R.C.P.Ed.

*Halton*

I PROPOSE to describe very briefly the "kidney" we use at Halton, and comment on conservative treatment and I shall then discuss the patients we have treated. We have performed 30 dialyses to date. The "kidney" and equipment weigh 538 lb. approximately. The assembly, testing and priming of the kidney takes about one hour. There is no sterilization of the unit to perform. The disposable units, i.e. artery and venous sets and the coil, are only used for one dialysis. 5 pints of fresh blood not more than five days old are required for priming and emergency use. The capacity of the kidney is about 1,000 ml. In order to eliminate any dead space we tense the cellophane with extra blood to a pressure of 250 mm.Hg just prior to connexion to the patient. All blood used through the kidney is heparinized. The patient is also given heparin before dialysis. To connect the patient to the kidney we use normally the radial artery—the blood returning to the median cubital, cephalic or saphenous veins. Polyvinylchloride cannulæ are employed.

Complications during dialysis have been few. Bleeding has been minimal; occasional oozing occurs from the sites of the "cutdown". A few cases develop hypotension, i.e. less than 100 mm.Hg systolic, which is controlled by small transfusions of 100 or 200 ml. of blood. We have not found any hæmolysis during dialysis. Little change has been noted in the patients' temperatures. On the whole we have found an improvement during dialysis. Some have regained consciousness dramatically, others have stopped vomiting, or convulsing—but all say they are very tired at the end of the six hours. In those patients we have weighed we may remove up to 3 litres of fluid from patients during dialysis. In 2 cases with pulmonary œdema, it has been greatly improved at the end of dialysis. The pressure in the blood circuit may be from 200 to 350 mm.Hg, and the flow rate 350 to 450 ml. per min. (an electronic flowmeter is used).

We endeavour if at all possible to avoid intravenous catheters, apart from the dialysis, due to the danger of introducing infection. Our conservative regime consists of an oral fluid intake (without intubation) equal to the urinary output and other losses plus 400 to 600 ml. for insensible loss in each twenty-four hours. We give at least 100 grams glucose a day but no fat, and in addition, vitamins, penicillin, and usually calcium gluconate daily. Bladder catheterization is reduced to an absolute minimum, self-retaining catheters are not used.

*General Indications for Hæmodialysis*

(1) Clinical deterioration, i.e. vomiting, twitching, convulsions, restlessness and clouding of the sensorium. If the patient's blood urea is 400 mg./100 ml. or more with this clinical state we would dialyse, but if the clinical state is reasonable a blood urea of 400 mg. or over would not, in our opinion, necessitate immediate dialysis, particularly if the patient has commenced a diuresis.

(2) An increasing hyperkalæmia of 7 mEq./l. or over, which does not respond to other measures.

(3) A serum bicarbonate of 12 mEq./l. or less.

We have found it wise to dialyse early rather than late, particularly in cases of multiple injuries or where there is much sepsis or tissue breakdown. There has been no death during dialysis.

I cannot envisage any specific condition which is a contra-indication to dialysis with this type of kidney. I have divided the cases treated by us into 4 groups as they presented on admission:

(1) Acute renal failures with reversible lesions.

(2) Acute renal failures with irreversible lesions.

(3) Chronic renal failures.

(4) Acute poisonings.

Of the 28 cases admitted to the unit 20 have been dialysed.

(1) Acute renal failures (reversible lesions) with tubular necrosis: 13 cases:
15 dialyses: 11 recovered from their renal failure. 10 are alive and well.
Obstructive lesions: 2 cases:
1 dialysis: 1 died of a non-renal lesion and 1 improved.
The artificial kidney is of most benefit in these cases.

(2) Acute renal failures (irreversible lesions): 8 cases:
8 dialyses: 7 died, 1 improved.

(3) Chronic renal failures: 4 cases:
4 dialyses: 2 died, 1 improved and 1 remains.

(4) Acute poisoning: 2 cases:

(i) Barbiturate (not in renal failure). Because he was unfit to move, the artificial kidney was moved to this patient's hospital and a successful dialysis of seven hours was performed. This is the first time an artificial kidney has been moved to another hospital in this country.

(ii) Carbon monoxide with muscle necrosis confirmed by biopsy. The patient had her second dialysis on October 2, 1958 and had recovered by early November.

*Advantages of the Kolff Twin Coil Kidney*

(1) It is easy and quick to assemble, and easy to operate.

(2) The parts are pre-sterilized.

(3) It produces ultrafiltration and removal of fluid in the œdematous and overhydrated patient.

(4) There is no potential dead space in the coils.

(5) The financial outlay is low.

(6) From the Service aspect it is mobile and can be transported with ease by road or air. It can be adapted with no difficulty for use in the field.

However, as Merrill (1955) pointed out, rightly, it is not so much the type of "kidney" used, but the experience of the team which is important. There is a considerable amount of detailed work required in the treatment of these cases, who are almost all in a desperate state on arrival. Adequate conservative treatment will guide most patients with acute renal failure through their illness. I must stress the point that the artificial kidney plays only a small part in the management of these cases and is in no way a substitute for good conservative treatment. Those cases most likely to require the assistance of the "kidney" are those with considerable tissue breakdown or sepsis, e.g. multiple injuries, a large involuting uterus, &c. There is no doubt now that the artificial kidney has a definite place in the treatment of selected cases of renal failure. Clinicians with cases of renal failure who are beginning to deteriorate should contact the nearest artificial kidney unit early, so that agreement can be reached as to the indications for transfer if necessary.

There are three artificial kidney units in constant use in this country. They are at:

(1) Leeds General Infirmary.

(2) Hammersmith Hospital.

(3) Princess Mary's Royal Air Force Hospital, Halton.

In addition St. Mary's Hospital, London, has recently received the same type of kidney that we use at Halton. The Royal Victoria Hospital, Newcastle-on-Tyne, has just received an Alwall kidney and the Western Infirmary, Glasgow, a Kolff twin coil kidney. The Royal Infirmary, Edinburgh, is to have a Kolff twin coil kidney in the near future.

REFERENCE: MERRILL, J. P. (1955) Treatment of Renal Failure. New York.

DISCUSSION

**Dr. F. M. Parsons** said that 128 patients had been treated in the Artificial Kidney Unit at the General Infirmary, Leeds, and 98 had been dialysed. In 15 patients the kidney lesion had been irreversible, and in many of these the onset of failure had been rapid. A bilateral ascending pyelogram should always be done before performing a percutaneous renal biopsy. In his opinion clinical deterioration was more important than the biochemical findings. The blood urea might be allowed to rise up to 400 or 500 mg./100 ml. if the patient was in a good physical state. Dr. Parsons doubted if a daily output of urine in excess of 1,000 ml. could always be taken as a positive criterion of recovery. At Leeds some patients had required dialysis when they were excreting daily amounts of urine well in excess of 1 litre. In discussing the best type of artificial kidney to use he suggested that a dialysis area of 30,000 sq. cm. was probably necessary for a severe case.

**Group Captain Jackson,** in reply to questions, said that the Royal Air Force had no experience of dialysing patients with extensive skin loss and agreed that this type of casualty would present technical difficulties which he considered could be overcome; the renal biopsies to which he referred were "needle" biopsies; and the operating team for the artificial kidney consisted of 2 medical officers and 2 sisters, but there were 4 medical officers attached to the Unit, supported by biochemists and other laboratory technicians.

**Dr. Joekes** agreed with Dr. Parsons that a daily output of 1 litre of urine was an entirely arbitrary criterion of recovery and was only one of the values to be considered in assessing whether or not a patient was recovering.

# Section of Endocrinology

President—Professor F. T. G. PRUNTY, M.D., F.R.C.P.

[*October* 22, 1958]

## The Interpretation of Hormonal Abnormalities

### PRESIDENT'S ADDRESS

By Professor F. T. G. PRUNTY, M.D., F.R.C.P.

*London*

IN 1934, when Sir Charles Dodds gave the Goulstonian Lectures, there were only three hormones under the control of the anterior pituitary, the chemical constitution of which was accurately known. Adrenaline was of course an addition to these. Additions which can now be made include at least 10 steroidal substances, with very numerous additional metabolites as well as insulin, tri-iodothyronine and nor-adrenaline and other hormones about which we have varying degrees of detailed information.

Knowledge of chemical structure is a sure foundation for the elaboration of good technical methods for the estimation of the hormones concerned. At the time of Dr. Parkes's Presidential Address to the Section (1950) the estimation of the hormones in blood was almost entirely a problem for the future. Nevertheless, in spite of the difficulties involved, he made a strong plea for greater attention to be paid to this question. It would be superfluous to mention all the hormones which can now be estimated in blood with an acceptable degree of accuracy, but they include some such as insulin, corticotropin and thyrotropin dependent still on bio-assay techniques, and others such as steroids and catechol amines where chemical methods may be accurately applied.

The rapid improvement in the chemical and physicochemical methods available is due particularly to development of chromatographic methods, especially the use of paper, and to the use of radioactive isotopic techniques. After many years' effort by many of us, and especially by Dr. R. K. Callow and later by Dr. B. W. Klyne, the work is greatly facilitated by the availability through the courtesy of the Medical Research Council of a large range of steroid reference substances. These chemically pure substances are required particularly in the establishment of the validity of analytical methods, as well as in many other ways.

More critical evaluation of the methods used whether chemical or biological is now expected and is a necessary requirement in the correct interpretation of analytical data. We must acknowledge a considerable debt to our colleagues in the Edinburgh School for their constant efforts in recent years to bring home to us the importance of this matter. It is now generally accepted that a reliable method should conform to rigid requirements of specificity, reproducibility, accuracy, sensitivity and then convenience. Lastly our knowledge of the normal has greatly increased and facilitates our interpretations.

Parallel with these advances in technology have come developments in the pathophysiology of many of the hormones which have important bearings on the interpretation of our data. That the truth of this assertion is only too obvious can be seen in the report of the valuable Ciba Colloquium held in 1957 on "Hormones in Blood". Hormone estimations are of great value to the clinical endocrinologist if they give information about the activity of the gland secreting the hormone and the amount of hormone activating the end organ or organs, thus producing clinical changes. For many years our thoughts have been confined to the direct relationship between this gland activity and the resulting end-organ effects, but it will be clear that the time has now arrived when a more critical evaluation of the situation must be made, and factors modifying this relationship assessed.

To begin with I should like to refer to an over-schematized diagram to indicate points for discussion (Fig. 1). Commencing at the top with the liberation of the hormone from the secreting gland into the blood stream, it may be present in the plasma in a form involving some kind of binding to protein. In most cases a large part of the hormone secreted is metabolized in some way in the liver and other tissues. Whilst a small proportion is excreted in the urine unchanged, metabolites are generally the main excretory products. Passage of the hormone from the blood via the tissue fluid occurs before ultimately reaching the end organ or target gland. There are a number of points (marked H in Fig. 1) where there is some evidence that the processes may be affected by other hormones simultaneously present in the system. Although even less is known of the subject, we must also be prepared for modifications to occur in the balance on account of the operation of nutritional and other factors.

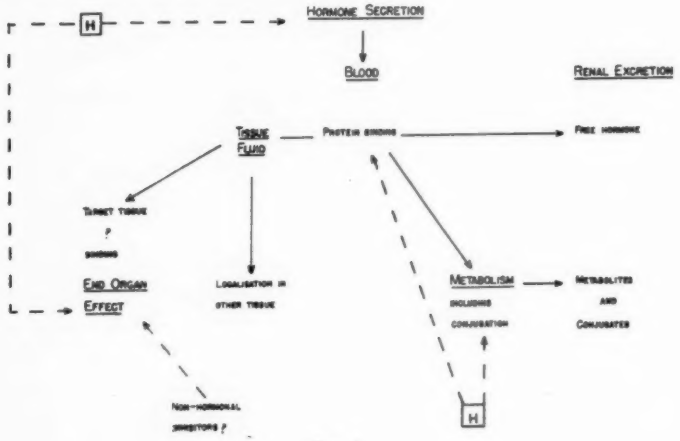



FIG. 1.

We are now approaching the time when measurements of secretion rate will become more commonplace and be practicable for clinical purposes. It must, however, be appreciated that quite frequently one may be concerned with conditions where hormone secretion is fluctuating at varying rates, depending upon the conditions and the glands involved. I have in mind such states as thyrotoxicosis, Cushing's syndrome, hyperparathyroidism, hyperinsulinism, &c., and we are especially interested in the times when the secretion rate is raised, rather than those when it may be normal. Present methods of determining the secretion rate may be divided into indirect and direct techniques. The measurement of the uptake rate of radioactive inorganic iodine and the amount liberated into the blood in protein-bound form is an example of the indirect method. It is well known that the interpretation of such changes is open to a variety of hazards if one wishes to deduce the actual rate of secretion and total amount of hormone liberated from the gland. Apart from problems associated with the size of the inorganic iodine pool, perhaps more important are those arising from enzymatic abnormalities in the synthesis of thyroid hormone in certain myxœdematous states, an analogous situation to that arising in the adrenal where corticoid synthesis may be blocked owing to the failure of hydroxylating enzymes which are required in the synthetic pathway.

In some instances secretion rates may be measured by more direct techniques. Firstly, calculations may be made on the basis of the amount of suitable metabolites excreted in the urine after the administration of a quantity of precursor. In this way Brown (1957) has been able to compute the secretion rate of œstradiol and œstrone throughout the normal menstrual cycle. One must be cautious in such interpretations for under some conditions the proportion of the metabolites formed from the parent hormone may undergo variations. Also the time taken to collect a sufficient quantity of metabolite may be long and the administration of sufficient quantity of precursor may interfere with the conditions to a material degree. By the administration of a small quantity of isotopically labelled precursor, necessitating only the determination of the specific activity of the chosen metabolite(s), these objections may be partially overcome.

Still better, in some instances, there is a more direct approach. The rate of decrease of

specific activity of the hormone may be determined in the plasma after injection of labelled hormone of known activity. With a knowledge of the actual hormone level at some stage during the measurement, and making several assumptions, the secretion rate may be calculated. Changes in the slope of decline of the specific activity in the plasma may be used as an indication of changes of secretion rate. Such a method is capable of indicating and confirming the diurnal variation of secretion of cortisol by the adrenal gland (Petersen and Wyngaarden, 1956).

The potential importance to the clinician of protein binding of hormones in the plasma is as yet difficult to assess. It influences the amount of hormone freely available on account of the avidity of binding, the availability of the protein to which the hormone is bound or possibly by competitive binding, for instance by different steroids. It has for some years been recognised that œstrogens undergo an association with proteins, but curiously enough the protein binding of these steroids has at present become a particularly controversial matter. More recent knowledge of thyroid and corticoid hormones appears to indicate that a proportion of the hormone is firmly bound to globulin, a further portion is more loosely bound to albumin, a kind of reserve overflow mechanism, and that quantities exceeding this capacity are freely available. Such a state of affairs would tend to limit the accumulation in the plasma of high concentrations of hormone. There is even evidence that polypeptides, such as the antidiuretic hormone, and thyrotropin are associated with plasma proteins. That cortisol concentration in extracellular fluid is below that of the plasma level is now well known (Cope and Hurlock, 1953).

Our knowledge of the fate of hormones in the tissues themselves is extremely scanty. In the case of insulin for instance some kind of association with muscle tissue occurs which may be an association with the protein of the tissue: it is not easily washed away from rat diaphragm preparations immersed in its solution. It would thus appear that in any consideration of the quantity of hormone reaching its site of action a complete series of equilibria must be envisaged in transference of the hormone from its site of secretion. Not only are the free hormones protein bound, but conjugates of corticoids, œstrogens and dehydroepiandrosterone are also known to be transported in this way in the plasma. At present it is difficult to see any obvious purpose in this but it leads me to mention the significance of hormone metabolism in our consideration of blood levels.

The general nature of metabolic inactivation is too widely recognised to dwell on this aspect, but oxidation, reduction, conjugation and other changes are general reactions which are well known to occur, largely in the liver. The limitation of the rate of these reactions, due to impairment of normal function of the liver in this respect, is leading to the emergence of a new type of endocrinological abnormality. The simple notions hitherto held concerning the role of the liver in producing clinical evidence of œstrogen excess, such as gynæcomastia, may well merit further investigation, but we also have for example the recently recognized occurrence of signs of excess of adrenal hormones in juvenile cirrhotics (Sherlock, 1958).

The new knowledge gained of the changes in adrenal hormones in pregnancy is of particular interest. The use of recent methods for measuring the amount of corticoid metabolites in the urine, principally conjugates, has indicated much less urinary increase of these steroids than had been observed with early techniques, which are now known to have measured mostly free steroids (Martin and Mills, 1958). Measurements of blood cortisol on the other hand made by them and of the turnover rate of $^{14}C$ cortisol have shown an increased blood level which is not apparently due to increased gland secretion and therefore is presumably due to decreased metabolism (Migeon *et al.*, 1957). This is perhaps the best example of a type of abnormality which justifies the most critical analysis of the significance of levels of hormones in the blood, or for that matter of urine excretion values. Although pregnancy has been referred to by some as a physiological Cushing's syndrome it is perhaps more remarkable that its resemblances to this syndrome are so slight! In this connexion it has recently been found that œstrogens have the effect of raising the level of cortisol in the blood, but in protein-bound and not free form (Mills *et al.*, 1958). We must also take into account the possibility that hormone metabolites, and not only the hormones themselves, may possess physiological functions. This is perhaps indicated for instance by the biological activities manifest by thyroxine degradation products, such as the pyruvic acids and their derivatives.

It is surprising that apparently such large quantities of waste products arise from the original hormone secreted. Thus the major part of steroid hormones secreted each day is lost in some form by renal excretion, and the major part of their degradation has apparently occurred in a way which is unrelated to its specific actions. The handling of hormones and their metabolites by the kidney is revealing itself as a complex and many-sided process. Steroid glucuronide complexes are apparently freely filtrable, whereas the clearance of dehydroepiandrosterone sulphate for instance is very much smaller. Similarly the

clearance of free corticoids is only a fraction of that of the glucuronide complexes. The relative roles of tubular reabsorption and protein binding in the production of this discrepancy are not yet known. To date knowledge of the renal pathology of hormone excretion has indicated chiefly the effect of filtration failure on the accumulation of conjugated steroids in the blood. In the case of cortisol there is also a smaller change in the free hormone which may be attributable to the level of the equilibrium with its metabolites (Englert *et al.*, 1958).

A little is known, however, of what happens to hormones remaining in the blood stream with respect to their availability to the tissues. A beginning has been made with the use of isotopically labelled hormones such as anterior pituitary hormones, progesterone and insulin to determine how they are localized. It seems that the proportions localized in the expected site may be small and larger quantities which in some instances appear in liver and kidneys may be undergoing metabolic breakdown. But surprises may well be coming. In a very recent report it was shown that tritium-labelled insulin was prominently localized in the anterior pituitary and adrenals (Holt and Holt, 1958).

Before we can interpret the blood level of a hormone in terms of its tissue effects we need to know something of the mode of action of the hormone in association with enzymes and therefore of the influence of other hormonal and non-hormonal factors on this process. The wasteful turnover of energy which can be excited by thyroxine is somewhat startling at first sight. Its physiological significance has been questioned (Pitt-Rivers, 1958) but it may have more important pathological implications. Enzymatic reactions in the synthesis of nucleoprotein and protein in the uterus are now known to be directly stimulated by œstrogen (Mueller *et al.*, 1958) as also is hydrogen transfer to diphosphopyridine nucleotide (Villee and Hagerman, 1958). It must be expected that such end reactions of hormones will be influenced in other ways than by the hormones themselves. Such factors may include nutritional ones, which are being increasingly recognized as being of importance in connexion with hormone production. The effects of severe malnutrition on atrophy of the reproductive organs is perhaps an extreme example but a nearer one is the ever intriguing problem of the reduced function of the endocrine system which may occur in anorexia nervosa. More specifically in the guinea-pig for example ascorbic acid deficiency may act as an inhibitor and then when more acute as an excitor of adrenal cortical function (Prunty *et al.*, 1957).

The amount of one particular hormone available may have repercussions upon the secretion of another. The effects under this heading of the "push-pull" principle are now taken as a matter of course, but the interaction may extend more widely than this. For instance we have recently found that under conditions where thyroid and corticotropin secretions are both reduced in the same patient the response to a constant replacement dose of corticotropin may be greatly enhanced by the simultaneous administration of tri-iodothyronine (Brooks, Hetzel, McSwiney and Prunty, 1957). The increased secretion of thyroid hormone not only increases the rate of cortisol secretion but also appears to increase its rate of metabolism (Cope and Black, 1958; Samuels *et al.*, 1957). We are not concerned with the specificity of the mode of action of the thyroid hormone in these effects, but the fact that there is an interdependence is of importance to us. The responsiveness of the female rat adrenal to corticotropin bears some relation to the amount of œstrogen available (Clayton and Hammant, 1957).

There are in addition effects of hormones on protein binding of other hormones, as for instance the alteration by œstrogen of thyroxine binding, and probably also on the metabolism of other hormones. Mention has already been made of the altered corticoid metabolism in pregnancy and it seems possible that œstrogens are also connected with this phenomenon.

One of the best examples of the complexity of hormone interaction is perhaps in the mammary gland, where under experimental conditions gland growth in the rat is influenced by at least 5 hormones, including a sufficiency of adrenal corticoid. This involved synergism reveals considerable possibilities in the phenomena at present loosely grouped under the heading of end-organ sensitivity. It is perhaps hardly surprising that our attempts to explain the occurrence of gynæcomastia in its various clinical settings are as yet so feeble. Problems such as this can now only be regarded as being in the stage of definition.

Another that is equally intriguing is the unresponsiveness of some individuals to large doses of androgens. This was touched upon by our President last year (Armstrong, 1958) and more recently by Hellinga (1958). I too have seen this phenomenon, for example in a hypergonadotropic eunuchoid, with female nuclear sex, who is apparently exceedingly refractory to testosterone therapy.

The last item of the diagrammatic scheme of blood hormone relationship is as yet perhaps the most speculative (Fig. 1). I refer to the problem of antihormones and do not mean

the type of resistance commonly recognized, to impure heterologous hormones, for instance the human unresponsiveness to growth hormones other than of human origin, but to true hormone inhibitors. An approach to this problem is currently being made in the case of insulin but we have as yet only a glimpse of the possibilities. Here again it seems that blood proteins may play an important role.

But much of what I have referred to must be regarded as an indication of the qualifications the clinician of the future must bear in mind when he interprets data of blood hormone levels in his patients. In spite of the complication of the subject, the clinical endocrinologist should count himself fortunate in comparison with some of his colleagues in other fields, in that there are already in existence so many measurable parameters to guide him in his problems of both diagnosis and therapy.

I would like now to consider several specific features of adrenal cortical abnormalities with which I have been recently concerned; it is hoped to publish more details elsewhere. In the first place data from a group of 11 patients considered to have primary aldosteronism have demonstrated that there was a considerable fluctuation in the day-to-day excretion of aldosterone. After allowing for this it did not seem possible to correlate the excretion levels either with the capacity for renal filtration or with the presence or absence of small adrenal cortical adenomas. Secondly there occurred in a few patients with Cushing's syndrome severe alkalosis, hypokalæmia and potassium depletion. Two patients were described who secreted excess cortisol but had little corticosterone in the plasma and excreted low normal quantities of aldosterone. Treatment of one of these with a pituitary implant of $^{90}Yt$ abolished the hypersecretion of cortisol and severe abnormality of potassium metabolism without reducing the aldosterone excretion farther. The occurrence of these changes in such patients and of similar changes in primary aldosteronism in instances where there was no detected hormone abnormality seems to raise the possibility that a hitherto unrecognized hormonal substance might be involved.

Some other unusual clinical findings in patients with increased hormone production by the adrenal cortex were then discussed. The first of these related to a patient in whom the usual stigmata of Cushing's syndrome were absent in spite of a marked increase of plasma hydrocortisone and urinary 17-ketogenic steroids produced from an adrenal carcinoma (Brooks, McSwiney, Prunty and Wood, 1957).

The second case also showed similar evidence of increased cortisol production and I am indebted to Dr. Edmunds and his colleagues for much of the information and photographs (Edmunds *et al.*, 1958). The patient was 42 and complained of lassitude and was somewhat overweight with impaired sugar tolerance but was not hypertensive. Apart from this, she showed none of the typical signs of Cushing's syndrome but a remarkable pigmentation had recently developed, involving the buccal mucosa and this together with the lassitude suggested to them the possibility of Addison's disease.

There was pronounced hypokalæmic alkalosis and a very large potassium deficit was demonstrable. She was found by Dr. Clayton to have a considerable excess of corticotropin in the plasma (Clayton, 1958, Patient C) but Professor Landgrebe was not able to demonstrate the presence of melanophore stimulating hormone (MSH).

Subtotal adrenalectomy was performed with complete reversal of all the patient's symptoms and signs, including disappearance of the abnormal pigmentation. The features of this case appear to contradict all the "laws" of endocrinology. There was bilateral adrenal hyperplasia involving only the fasciculata and from the biochemical point of view the conditions were typical of those of Cushing's syndrome. The pigmentary changes are quite inexplicable on current theories, indeed if corticotropin and not MSH was involved in the pigment formation one is at a loss to understand the decrease of pigment after adrenalectomy, when it would be expected that even more corticotropin might be secreted. Unfortunately, we have not as yet any information on the corticotropin level in the blood following adrenalectomy.

The existence of another interesting group of patients has recently been emphasized by Kovach and Kyle (1958). These are individuals with a fulminating type of Cushing's syndrome due to adrenal hyperplasia, and frequently with disturbances of potassium metabolism, in whom are also found bronchial oat cell carcinomas. Some details were given of the author's personal experience of one of the first of this group of patients, who at the time was regarded as a medical curiosity, and was one of the two patients reported by Thorne (1952).

Finally very recent studies of another aspect of adrenal abnormality in young women with hirsutism (Prunty *et al.*, 1958) were discussed. It would seem that there is reasonable evidence to suppose that there is some degree of adrenal abnormality in the Stein-Leventhal syndrome, a greater degree in some patients with simple hirsutism, a still greater degree in some occasional women developing signs of virilism after puberty (Prunty *et al.*, 1958) and a maximal degree in patients with congenital adrenal hyperplasia. It still remains to

be determined how far these patients differ in kind rather than degree. Although we are left with the impression that there is no indication of an ovarian androgen in the Stein-Leventhal patients, we still have to take into account the consequences of the secretion of small amounts of a very active androgen such as testosterone. It is quite possible for this, or some unknown androgen, to be secreted in amounts sufficient to cause signs of virilization in sensitive persons and yet in quantities insufficient to be detected by our methods as any of the metabolites we have examined. Such a state of affairs would offer a better explanation of our findings which could be taken as indicating metabolic disturbances accompanying but not directly indicating the fundamental abnormality.

I have discussed these adrenal abnormalities at some length because of the interesting problems they present and because they do not appear to be entirely explicable in the light of current knowledge. The ability to carry out hormone assays would seem in the beginning to confirm preconceived ideas because we naturally tend to apply them in circumstances where we expect to find a postulated abnormality. As we proceed less typical situations are discovered and some of them no doubt must lead us to question the complete validity of our original ideas. The evolution of such developments is the essence of progress.

## REFERENCES


ARMSTRONG, C. N. (1958) *Proc. R. Soc. Med.*, **51**, 23.

BROOKS, R. V., HETZEL, B. S., MCSWINEY, R. R., and PRUNTY, F. T. G. (1957) *J. Endocrin.*, **15**, 320.

——, MCSWINEY, R. R., PRUNTY, F. T. G., and WOOD, F. J. Y. (1957) *Amer. J. Med.*, **23**, 391.

BROWN, J. B. (1957) *J. Endocrin.*, **16**, 202.

Ciba Foundation (1957) *Ciba Found. Coll. Endocrin.*, **11**.

CLAYTON, B. E. (1958) *Proc. R. Soc. Med.*, **51**, 558.

——, and HAMMANT, J. E. (1957) *J. Endocrin.*, **15**, 255.

COPE, C. L., and BLACK, E. (1958) *Brit. med. J.*, i, 1020.

——, and HURLOCK, B. (1953) *Brit. med. J.*, ii, 753.

DODDS, E. C. (1934) *Lancet*, i, 1048.

EDMUNDS, A. W. B., MCKEOWN, K. C., and COLEMAN, P. N. (1958) *J. clin. Path.*, **11**, 3.

ENGLERT, E., BROWN, H., WILLARDSON, D. G., WALLACH, S., and SIMONS, E. L. (1958) *J. clin. Endocrin.*, **18**, 36.

HELLINGA, C. (1958) *Acta endocr., Copenhagen*, **28**, Suppl. 38, 65.

HOLT, C. v., and HOLT, L. v. (1958) *Acta endocr., Copenhagen*, **28**, 86.

KOVACH, R. D., and KYLE, L. H. (1958) *Amer. J. Med.*, **24**, 981.

MARTIN, J. D., and MILLS, I. H. (1958) *Clin. Sci.*, **17**, 137.

MIGEON, C. J., BERTRAND, J., WALL, P. E., STEMPFEL, R. S., and PRYSTOWSKY, H. (1957) *Ciba Found. Coll. Endocrin.*, **11**, 338.

MILLS, I. H., SCHEDEL, H. P., REDD, D., and BARTTER, F. C. (1958) *Proc. Endocrine Soc.*, p. 27.

MUELLER, G. C., HERRANEN, A. M., and JEWELL, K. F. (1958) *Recent Prog. Hormone Res.*, **14**, 95.

PARKES, A. S. (1950) *Proc. R. Soc. Med.*, **43**, 361.

PETERSEN, R. E., and WYNGAARDEN, J. B. (1956) *J. clin. Invest.*, **35**, 552.

PITT-RIVERS, R. (1958) In: Modern Trends in Endocrinology. Ed.: H. Gardiner-Hill. London: p. 1.

PRUNTY, F. T. G., BROOKS, R. V., and MATTINGLY, D. (1958) *Brit. med. J.* In press.

——, CLAYTON, B. E., and HAMMANT, J. E. (1957) *Ciba Found. Coll. Endocrin.*, **11**, 150.

SAMUELS, L. T., BROWN, H., EIK-NES, K., TYLER, F. H., and DOMINGUEZ, O. V. (1957) *Ciba Found. Coll. Endocrin.*, **11**, 208.

SHERLOCK, S. (1958) *Proc. R. Soc. Med.*, **51**, 359.

THORNE, M. C. (1952) *Guy's Hosp. Rep.*, **101**, 251.

VILLEE, C. A., and HAGERMAN, D. D. (1958) *J. biol. Chem.*, **233**, 42.

e are
Stein-
on of
this,
ation
s any
ation
nying

esting
light
nning
ances
ations
lidity

5, 320.
3, 391.

*l. clin.*

) *Ciba*

p. 27.
14, 95.

ndon:

) *Ciba*

DOES NOT CIRCULATE

VOLUME 51 NUMBER 12 DECEMBER 1958

# PROCEEDINGS
## *of the*
# ROYAL
# SOCIETY OF MEDICINE

UNIVERSITY OF MICHIGAN
MEDICAL LIBRARY
DEC 30 1958




*Published by*
THE ROYAL SOCIETY OF MEDICINE, 1 WIMPOLE STREET, LONDON, W.1

*All rights reserved*

In all types of insomnia, CARBRITAL* secures a full night's refreshing sleep, with a fresh awakening on the morrow. Rapid onset of sleep is obtained by incorporating in the CARBRITAL formula a moderate dose of the quick-acting hypnotic, pentobarbitone sodium. This action is prolonged by the use of carbromal, a milder long-acting sedative, which maintains sleep for up to eight hours, leaving the patient with the minimum of depression on awakening.



# IN ALL TYPES OF INSOMNIA

*quick action*

*prolonged sedation*

*minimal after-effects*



# CARBRITAL

*Trade Mark

Capsules: In bottles of 25 and 250 capsules, each containing pentobarbitone sodium (1½ grs.) and carbromal (4 grs.)
Elixir: in bottles of 4, 16 and 80 fl. ozs. Each fluid drachm (one teaspoonful) represents pentobarbitone sodium (¼ gr.) and carbromal (½ gr.)

PARKE, DAVIS & CO. LTD. (*Inc. USA*), Hounslow, Middlesex. Tel: Hounslow 2361

# PROCEEDINGS

## of the

# ROYAL SOCIETY OF MEDICINE

ISSUED UNDER THE DIRECTION OF THE EDITORIAL COMMITTEE



HONORARY EDITORS

E. C. WARNER SELWYN TAYLOR

EDITORIAL REPRESENTATIVES OF SECTIONS

O. P. DINNICK (Anæsthetics)
RICHARD ASHER (Clinical)
M. CRAWFORD (Comparative Medicine)
D. I. WILLIAMS (Dermatology)
F. T. G. PRUNTY (Endocrinology)
J. KNOWELDEN (Epidem. and Preventive Med.)
A. C. WHITE (Exper. Med. & Therap.)
L. CARLYLE LYON (General Practice)
Sir ZACHARY COPE (History of Medicine)
F. C. W. CAPPS (Laryngology)
PHILIP ELLMAN (Medicine)
MACDONALD CRITCHLEY (Neurology)
W. C. W. NIXON (Obstetrics and Gynæcology)
J. H. HOVELL (Odontology)
S. J. H. MILLER (Ophthalmology)
T. J. FAIRBANK (Orthopædics)
G. H. BATEMAN (Otology)
D. MacCARTHY (Pædiatrics)
B. W. LACEY (Pathology)
W. S. TEGNER (Physical Medicine)
HAROLD DODD (Proctology)
Sir PAUL MALLINSON (Psychiatry)
A. M. RACKOW (Radiology)
D. H. PATEY (Surgery)
Surg. Cdr. F. P. ELLIS (United Services)
A. CLIFFORD MORSON (Urology)

SECRETARY OF THE ROYAL SOCIETY OF MEDICINE

R. T. HEWITT



**All correspondence to**

**THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1 (Tel: LANgham 2070)**

*Distributing Agents:*

H. K. LEWIS & Co. LTD., 136 GOWER STREET, LONDON, W.C.1

*In the U.S.A.:*

GRUNE & STRATTON, INC., 381 FOURTH AVENUE, NEW YORK 16

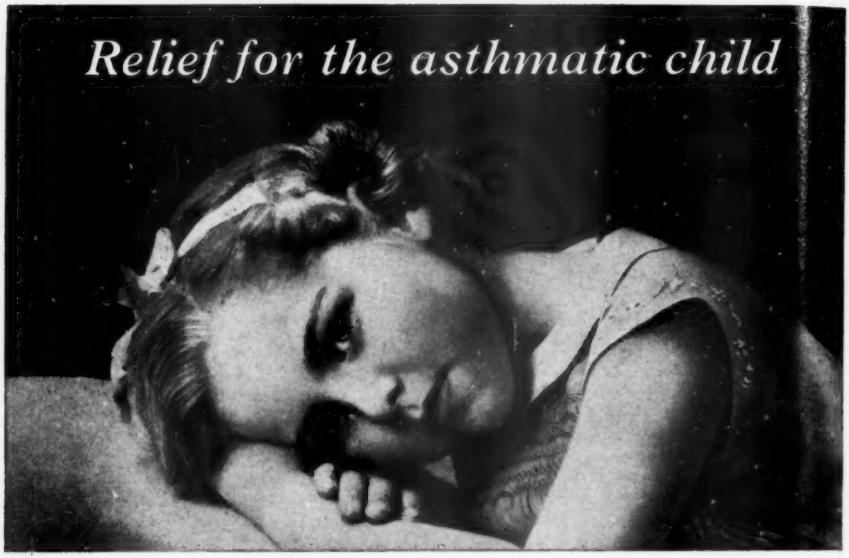
*Advertisement Managers:*

H. S. JANES & PARTNERS LTD., 99, GOWER STREET, LONDON, W.C.1

*Telephone:* EUSton 3221

Monthly, 10s. 6d. net. Annual Subscription, £6 6s. in the British Commonwealth, $19.00 in the U.S.A.

53




## UNIQUE BUFFERED THEOPHYLLINE SYRUP

Relief from the apprehension and acute distress of an asthmatic attack is provided by 'ENGLATE.' In almost all cases gastrointestinal disturbance is entirely absent. The combination of theophylline sodium with glycine permits full and effective therapeutic activity and by reducing gastric precipitation of theophylline enables larger doses to be prescribed.

**ENGLATE**
*Trade Mark* — *Theophylline Sodium Glycinate*

*Samples and literature will gladly be sent on request*

**SYRUP** (containing 120 mg. of theophylline sodium glycinate per 4 ml.) for children up to 12 years. Available in bottles of 8 fluid ounces.

**TABLETS** (300 mg. of theophylline sodium glycinate). Available in bottles of 50 and 500.

A Nicholas Product

**Aspro-Nicholas Ltd.** *Slough, Bucks, England*
*(Ethical Pharmaceutical Division)*

PROCEEDINGS
OF THE
ROYAL SOCIETY OF MEDICINE

Vol. 51 No. 12 December 1958

## CONTENTS

| | Whole Proceedings Page |
|---|---|
| **Section of Neurology** | |
| Endogenous Hypoglycæmia.—President's Address by HUGH GARLAND, T.D., M.D., F.R.C.P. | 979 |
| **Section of Laryngology** | |
| A Possible Relationship Between the Sinuses and the Lymphoid Tissue of the Nasopharynx.—A. J. MOFFETT, T.D., F.R.C.S. | 991 |
| **Section of Laryngology with Section of Otology** | |
| JOINT SUMMER MEETING HELD AT THE ROYAL COLLEGE OF SURGEONS OF EDINBURGH *June* 27, 1958. Discussion (*By Title*). *June* 28, 1958. Discussion (*By Title*) | 995 |
| **Books Received for Review. Books Recently Presented and Placed in the Society's Library** | 996, 1054 |
| **Section of Experimental Medicine and Therapeutics with Section of Neurology** | |
| JOINT MEETING NO. 2. DISCUSSION ON TETANUS | 997 |
| **Section of Epidemiology and Preventive Medicine** | |
| JOINT MEETING WITH THE FEVER GROUP OF THE SOCIETY OF MEDICAL OFFICERS OF HEALTH SYMPOSIUM ON THE ASIAN INFLUENZA EPIDEMIC, 1957 | 1009 |
| **Section of Pædiatrics.** MEETING HELD AT BRISTOL | |
| The Treatment of Phenylketonuria.—F. S. W. BRIMBLECOMBE, M.D., and MARGARET E. R. STONEMAN, M.B. | 1019 |
| Hyperbilirubinæmia in Premature Infants Treated by Exchange Blood Transfusion.—BERYL D. CORNER, M.D., F.R.C.P. | 1019 |
| Heart Failure in Infants.—K. SIMPSON, M.D. | 1022 |
| A Common Denominator in the Recurrent Pains of Childhood.—JOHN APLEY, M.D. | 1023 |
| The Vascular Factor in Birth Injury.—A. V. NEALE, M.D., and H. URICH, M.D. | 1024 |
| DEMONSTRATIONS | 1025-1028 |

*Continued overleaf*

**In hepatic conditions . . .**

In hepatic conditions, when a reserve of liver glycogen and the speedy ingestion of nourishment are of supreme importance, Lucozade is strongly indicated. Its many-sided appeal ensures immediate acceptance; and the fact that the patient will easily take as much as is necessary ensures an adequate blood sugar level in the shortest possible time.

Lucozade is lightly carbonated with an attractive golden colour and a pleasant citrus flavour. It contains 23·5% w/v Liquid Glucose B.P., and its energy value is 21 calories per fluid ounce. It is supplied in 6 oz. and 26 oz. bottles.

**LUCOZADE**

## CONTENTS (*continued*)


| | Whole Proceedings Page |
|---|---|
| **Section of Urology.** *April* 25, 1958, contd. MEETING AT THE GENERAL INFIRMARY, LEEDS Elective Prostatectomy.—Professor E. WILDBOLZ .. .. .. .. .. | 1029 |
| *May* 22, 1958. VESICO-INTESTINAL FISTULA [*Abridged*] .. .. .. .. .. | 1032 |
| **Section of Orthopædics.** MEETING AT ROYAL NATIONAL ORTHOPÆDIC HOSPITAL, STANMORE Osteotomy in the Treatment of Congenital Dislocation of the Hip [*Abridged*].—DAVID TREVOR, M.S., F.R.C.S. .. .. .. .. .. .. .. | 1043 |
| **Section of Pathology.** [AMENDMENT] .. .. .. .. .. .. .. .. | 1048 |
| **Section of the History of Medicine** A Manuscript of Benjamin Collins Brodie's Surgical Lectures, 1822; with Some Notes on the History of Stricture and Stone.—Sir ERIC RICHES, M.C., M.S., F.R.C.S. .. | 1049 |
| **Section of Odontology** Research, Organization and Teaching in Forensic Odontology.—GÖSTA GUSTAFSON, Dr.odont., F.D.S. R.C.S.Ed. .. .. .. .. .. .. .. .. | 1055 |
| The Assessment of Age from the Dentition.—A. E. W. MILES, F.D.S., L.R.C.P., M.R.C.S. .. .. .. .. .. .. .. .. .. .. | 1057 |
| **Book Reviews** .. .. .. .. .. .. .. .. .. .. .. | 1061 |
| **Section of Medicine.** The Development of the Treatment of Duodenal Ulcer [*Abridged*].—President's Address by A. H. DOUTHWAITE, M.D., F.R.C.P. .. .. .. | 1063 |
| **United Services Section** A Review of Hæmodialysis in Renal Failure and Some Points in the Diagnosis of Acute Renal Failure.—A. M. JOEKES, M.R.C.P. .. .. .. .. .. | 1069 |
| Experiences with the Kolff Twin Coil Artificial Kidney at the Renal Unit, Princess Mary's Royal Air Force Hospital, Halton.—Group Captain R. C. JACKSON, M.R.C.P.Ed. .. .. .. .. .. .. .. .. .. .. | 1071 |
| **Section of Endocrinology.** The Interpretation of Hormonal Abnormalities.—President's Address by Professor F. T. G. PRUNTY, M.D., F.R.C.P. .. .. .. .. | 1073 |


*N.B.—The Society does not hold itself in any way responsible for the statements made or the views puts forward in the various papers.*

**Copyright:** The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors, Royal Society of Medicine .... The copyright of all papers presented at meetings by Fellows of the Society or Members of the Sections (other than those which have been previously published) shall be deemed to be the property of the Society until a decision has been made by the Society in regard to their publication.


# A History of Medicine

*Revised Edition* *by* **DOUGLAS GUTHRIE**

This book has become the standard work on its subject. Now, after thirteen years, a thoroughly revised edition will be welcomed by doctors, medical students, and the inquiring general reader. The text has been completely revised in the light of recent research, and many new references have been added. The new material includes comprehensive notes on herbals and pharmacopoeias, on witches and witch-hunting, mesmerism, and the history of nursing. 72 halftone plates.

$8\frac{3}{4} \times 5\frac{5}{8}$ *xvi + 464 pp* *42s*

## HISTORY OF THE ROYAL MEDICAL SOCIETY

**1737—1937** *by* **JAMES GRAY MA FRSE**

This is the first detailed history of the oldest medical society in Great Britain from the time of its foundation until the bicentenary celebrations in 1937. *Illustrated* *Edinburgh University Press* *42s*

***Prospectuses available from 36 Park Street London W1***

**NELSON**



# Ames

## ROUTINE URINE TESTS

*—reliable, quick, no external heating—*

A **NEW** COLOUR TEST

For **PROTEIN** ———— ***ALBUSTIX**
*reagent strips*

For **BLOOD** ———— ***OCCULTEST**
*reagent tablets*

For **GLUCOSE** ———— ***CLINISTIX**
*reagent strips*

For **BILIRUBIN** ———— ***ICTOTEST**
*reagent tablets*

For **KETONES** ———— ***ACETEST**
*reagent tablets*

*. . . and, of course, for reliable estimation of*

**SUGAR** ———— ***CLINITEST**
*reagent tablets*

Range of six simplified urine tests for General Practitioners, hospitals, clinics and laboratories.
*Please write for illustrated leaflet and references.*
'Acetest' and 'Clinitest' are available under the N.H.S. on form E.C.10. *(See drug tariff)*
**Trade Marks*

**AMES COMPANY (LONDON) LTD**
NUFFIELD HOUSE, PICCADILLY, LONDON, W.1 · *Telephone: REGent 5321*

## *Important Livingstone Books*

**TUMOURS OF THE BLADDER**
Edited by D. M. WALLACE, *O.B.E.*, M.S., F.R.C.S.
364 *pages.* 249 *illustrations.* **60s.**

**STAPHYLOCOCCUS PYOGENES AND ITS RELATION TO DISEASE**
By STEPHEN D. ELEK, M.D., Ph.D., D.Sc., D.P.H.
775 *pages.* 81 *illustrations.* **84s.**

**TEXTBOOK OF PHYSIOLOGY AND BIOCHEMISTRY**
*Fourth Edition.* By G. H. BELL, M.D., B.Sc., F.R.S.E., J. N. DAVIDSON, M.D., D.Sc., F.R.I.C., F.R.S.E., and H. SCARBOROUGH, M.B., Ph.D., F.R.C.P.E.
1,076 *pages.* 825 *illustrations.* **63s.**

**UROLOGY IN OUTLINE**
By T. L. CHAPMAN, Ch.M., F.R.C.S., F.R.F.P.S.G.
184 *pages.* 675 *illustrations.* **27s. 6d.**

**ORAL HISTOPATHOLOGY**
**A Manual for Students and Practitioners of Dentistry**
By M. A. RUSHTON, M.D., F.D.S.R.C.S., and BRIAN E. D. COOKE, M.R.C.S., L.R.C.P., F.D.S.R.C.S.
198 *pages.* 214 *illustrations.* **30s.**

**THE COMPARATIVE ANATOMY AND PHYSIOLOGY OF THE NOSE AND PARANASAL SINUSES**
By SIR VICTOR NEGUS, M.S., F.R.C.S.
418 *pages.* 390 *illustrations.* **70s.**

**CARCINOMA OF THE LUNG**
J. R. Bignall. **55s.**

**DISEASES OF THE NERVOUS SYSTEM**
*Ninth Edition.* Sir Francis Walshe. **30s.**

**THE INTERFERENCE MICROSCOPE IN BIOLOGICAL RESEARCH**
Arthur J. Hale. **20s.**

**LEPTOSPIROSIS IN MAN AND ANIMALS**
J. M. Alston and J. C. Broom. **40s.**

**HANDBOOK OF TREATMENT OF ACUTE POISONING**
*Second Edition.* E. H. Bensley and G. E. Joron. **15s.**

**TEXTBOOK OF MEDICAL TREATMENT**
*Seventh Edition.* Professors D. M. Dunlop, Sir Stanley Davidson and S. Alstead. **55s.**

**SCOTTISH SOCIAL WELFARE 1864-1914**
Professor Thomas Ferguson. **42s.**

**SIR CHARLES BELL: HIS LIFE AND TIMES**
Sir Gordon Gordon-Taylor and Professor E. W. Walls. **42s.**

**E. & S. LIVINGSTONE LTD., TEVIOT PLACE, EDINBURGH**

PM

## SKIN GRAFTING

James Barrett Brown, M.D., Professor of Clinical Surgery, Washington University and Frank McDowell, M.D., Associate Professor of Clinical Surgery, Washington University.

A new, revised and completely up to date third edition of the well-known work which has been out of print for some years. This edition greatly enhances the scope of the successful earlier editions. The material covers the entire field of traumatic injuries producing skin loss. Beautifully produced. Well illustrated. An important book. **£5 5s. 0d. net**

## PRINCIPLES OF RESEARCH IN BIOLOGY AND MEDICINE

Dwight J. Ingle, Professor of Physiology, Ben May Laboratory for Cancer Research, University of Chicago.

A clear and wise introduction to the principles and philosophy of research. Emphasis is placed on the difficulties and pitfalls to be recognised in the laboratory and on the need for clear thinking. The author makes his points with the help of trenchant quotation from the works of Lewis Carroll. Wise, witty, clear and packing several punches, this will be a most valuable book for the young research worker. **30s. net**

## THE MATRIX OF MEDICINE

Edited by Nicolas Malleson, M.D., with 15 Contributors.

A series of studies, by a distinguished team of writers, into some of the social aspects of modern medical practice. Investigates several of the borderlands between medicine and society. A lively and absorbing book. **45s. net**

**PITMAN MEDICAL PUBLISHING CO. LTD.**
39 PARKER STREET · LONDON · W.C.2

*Oxford* OXFORD MEDICAL PUBLICATIONS *University Press*

*To be published January 1959*

## A Clinical Introduction to Heart Disease

**CRIGHTON BRAMWELL** *Emeritus Professor of Cardiology in the University of Manchester; Consulting Physician to the Manchester Royal Infirmary*

This book has been written specially for general practitioners and senior students who intend to enter general practice. No attempt has been made to cover the whole field of cardiology: instead Professor Bramwell has paid particular attention to those problems in which—based on his own wide experience—the general practitioner most needs help. His aim throughout has been to discuss the diagnosis, treatment and prognosis of patients with heart disease in their own homes, by their own family doctor, and nearly all the methods given can be carried out without special equipment or hospital facilities. A valuable feature is the series of case histories—fully illustrated by x-rays and electrocardiographic tracings—that accompany nearly every condition described.

Demy 8vo 230 pages 61 illustrations 21s. net

## Pharmacology

**J. H. GADDUM, F.R.S.** *Director of the Institute of Animal Physiology, Cambridge, formerly Professor of Pharmacology in the University of Edinburgh*

*FIFTH EDITION*

Not only has the text of this new edition been very thoroughly revised; it has also been thoroughly but judiciously pruned. All the important drugs in the B.P. 1958 or in the U.S.P. have been included, as well as many new drugs that are not yet official. Wherever they are applicable Official Titles or Approved Names have been used, followed by other well recognised pharmacological names, proprietary names—printed in italic—and full chemical names. An innovation is the inclusion of metric doses for all official drugs—and for the majority of unofficial drugs—mentioned in the text.

Demy 8vo 586 pages 93 illustrations 42s. net

## Medical Museum Technology

**J. J. EDWARDS** *Chief Technologist, The London Hospital Medical College Museum* and **M. J. EDWARDS**

Medical museum technology has been interpreted here as comprising the preservation of all forms of tissue for teaching purposes or for research: it is not restricted solely to pathological material. This book describes in a practical way all aspects of the subject and, although all current techniques of importance have been included and most new methods noted, full descriptions have been reserved, largely, for techniques that have withstood the test of time. The history of museum technology is given at some length in the early chapters as it is hoped that an account of the lines on which techniques have developed will enable readers to appreciate more fully the descriptions of current techniques that follow.

Demy 8vo 180 pages 41 illustrations 21s. net

## A TEXT-BOOK OF X-RAY DIAGNOSIS

By British Authors. Edited by S. COCHRANE SHANKS, C.B.E., M.D., F.R.C.P., F.F.R., and PETER KERLEY, C.B.E., C.V.O., M.D., F.R.C.P., F.F.R., D.M.R.E.

*New (Third) Edition.* In Four Volumes. 10 in. x 7½ in.

Vol. I. **Head and Neck.**—533 pp. with 533 illustrations. **£4 10s.** net.
Vol. II. **The Cardiovascular and Respiratory Systems.**—In Preparation.
Vol. III. **The Abdomen.**—899 pp. with 802 illustrations. **£6** net.
Vol. IV. **Bones and Joints and Soft Tissues.**—Ready in the Spring 1959.

## THE MANAGEMENT OF ABDOMINAL OPERATIONS

Edited by RODNEY MAINGOT, F.R.C.S.(Eng.), with the assistance of 31 Contributors.
**New (Second) Edition.** In Two Volumes with 540 illustrations. 9½ in x 6 in. **£8** net.

## DISEASES OF THE THROAT, NOSE AND EAR

Edited by F. W. WATKYN-THOMAS, F.R.C.S.(Eng.), with the assistance of 10 Contributors.
With 367 illustrations. 10 in. x 6¾ in. **£5 10s.** net.

## TESTS FOR COLOUR-BLINDNESS

By SHINOBU ISHIHARA, M.D., Dr.Med.Sc., Emeritus Professor of Ophthalmology, Tokyo University.
**Thirteenth Edition.** 38 Plates with Instructions and Key. **£4** net; postage 1s. 9d.

**H. K. LEWIS & Co. Ltd.** **136 Gower Street, London, W.C.1**
Telephone: EUSton 4282. Telegrams: Publicavit, Westcent. London.

*"Recommended to every optician, essential in all consulting rooms for the treatment of Amblyopia in children."*

## THE AMBLYOPIA PICTORIAL TRACER

**By MARGARET DOBSON, M.D. (London)**

**Complete with Ruby filter and full details for use.**

**Price 45/-** (Postage extra)

**Also:**

## THE AMBLYOPIA READER

**By MARGARET DOBSON, M.D. (London)**

A method of training an Amblyopic eye, while at the same time interesting children in familiar stories.

The book is printed in black and orange and is read while the child is wearing a coloured filter over the sound eye.

Complete with filter and description of the method of training advised by the inventor, Dr. M. Dobson.

**Price 30/-** (Postage extra)

*Obtainable from:*
**THEODORE HAMBLIN**
**15 Wigmore Street, London, W.1**

## NOTICE TO ADVERTISERS

*Applications for advertisement space in the "Proceedings" should be made to:*

**H. S. JANES & PARTNERS**
LIMITED
**99 GOWER STREET, LONDON, W.1**
TELEPHONE: EUSTON 3221

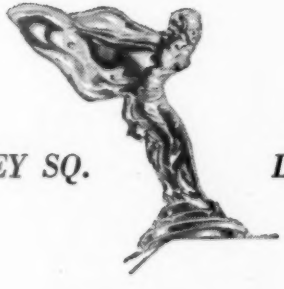
*The World's Largest Officially Appointed Retailer exclusive to*

ROLLS-ROYCE and BENTLEY Cars



# Jack BARCLAY

LIMITED



*BERKELEY SQ.* *LONDON, W.1*

*Mayfair 7444*

# "Aspirin is a serious gastric irritant, particularly in peptic ulcer patients"*

# "Calcium aspirin... can be used with impunity"*

**Extracts from B.M.J., 2-7-55*

## SOLPRIN is accordingly often prescribed

Solprin contains aspirin in soluble form. It is a highly efficient analgesic—the more quickly and easily absorbed by reason of its solubility. Dissolved in water, the tablets produce a solution of calcium acetylsalicylate. Solprin is extremely well tolerated, even by sufferers from peptic ulcer.

Solprin will be found particularly valuable when heavy or prolonged dosage is called for. Patients find Solprin easy to take and palatable.




**SOLPRIN** REGD.

Soluble and substantially neutral

*Not advertised to the public*

**Solprin is available only on prescription and only in Great Britain and Northern Ireland. Clinical samples and literature will be supplied on request.**

**N.H.S. BASIC PRICE 12/6 for 500 tablets in foil**

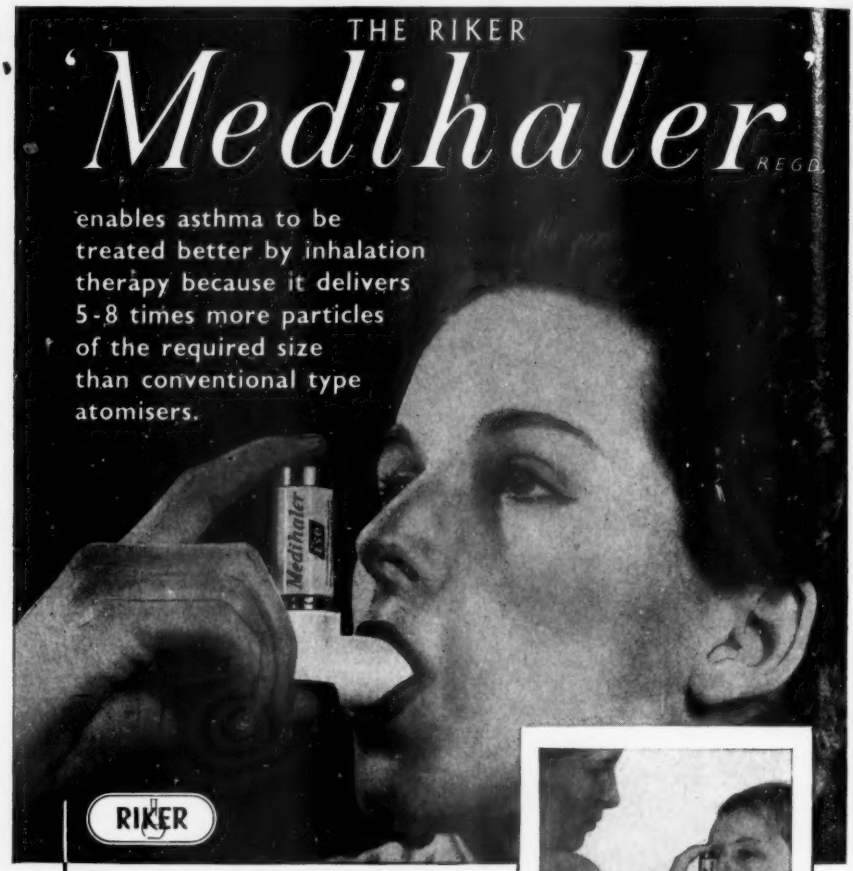
RECKITT & SONS LTD., HULL & LONDON (PHARMACEUTICAL DEPT., HULL)


Iron
patients
can tolerate...
Rarical
TRADE MARK
iron-calcium tablets
a unique new compound —
iron plus calcium in a single molecule
TOLERATED no stomach upset, constipation or diarrhoea
phosphate-free — no leg cramps
EFFECTIVE more haemoglobin in less time
EASY TO TAKE white, uncoated, tasteless tablets may be swallowed, chewed, or crushed and suspended in fluids
Each tablet provides: iron: 25mg. calcium: 88mg.
LITERATURE ON REQUEST
Ortho
Ortho Pharmaceutical Limited
High Wycombe · England
100
Rari
IRON – CAL
TABL

THE RIKER

# 'Medihaler' REGD.

enables asthma to be treated better by inhalation therapy because it delivers 5-8 times more particles of the required size than conventional type atomisers.






- ✳ **Measured dose of predetermined particle size.**
- ✳ **Aerosol spray mechanism.**
- ✳ **Extreme simplicity and ease of operation.**
- ✳ **Very robust mechanism.**
- ✳ **Ideal for children.**

**PRESCRIPTION INFORMATION**

The first prescription should order a Complete Outfit of either 'Medihaler' Epi or 'Medihaler' Iso (propellent unit and oral adapter). The basic N.H.S. cost is 12/8d. Repeat prescriptions should specify the appropriate refill propellent unit required. The basic N.H.S. cost is 10/4d.
'Medihaler' can be prescribed as complete outfits, and as refills. The oral adapter is included in the Drug Tariff.

*'Medihaler' is a registered trade mark.*

## 'Medihaler' EPI

*Contains 7 mg./cc. Adrenaline Acid Tartrate B.P. in suspension in inert aerosol propellent. Dose delivered is equivalent to 0.15 mg. adrenaline base.*

## 'Medihaler' ISO

*Contains 2 mg./cc. Isoprenaline Sulphate B.P. in inert aerosol propellent. Dose delivered is 0.075 mg. isoprenaline sulphate.*

**RIKER LABORATORIES LIMITED LOUGHBOROUGH LEICS.**

*'Inversine' and 'Saluric' introduce a New Era in the treatment of Hypertension*

'SALURIC', already universally accepted as the only oral diuretic as effective as mersalyl, possesses the *unique* and *additional* property of *hypotensive activity*. Frequently it may be possible to control blood pressure with 'SALURIC' *alone* or with the addition of only a sedative or mild hypotensive agent. But when ganglion blocking agents are required in addition, the dosage and administration of these is greatly simplified.



# LONGER LIFE FOR HYPERTENSIVES

'INVERSINE' and 'SALURIC' *concurrently*, provide: Smaller dosage of 'INVERSINE'; Smoother control of blood pressure; Freedom from, or diminution in, side-effects usually associated with ganglion blockade.

*How supplied:*

'INVERSINE': 10 mg. tablets (white, quarter-scored); 2.5 mg. tablets (yellow, half-scored).

'SALURIC': 0.5 G. tablets (half-scored).

*'Inversine' and 'Saluric' are* not *supplied in a combined tablet.*

*'INVERSINE' and 'SALURIC' were discovered and developed in the Merck Sharp & Dohme Research Laboratories, and are manufactured in England exclusively by the Merck Sharp & Dohme Organisation. 'Inversine' and 'Saluric' are Registered Trade Marks.*

**Inversine**
MECAMYLAMINE HYDROCHLORIDE

**Saluric**
CHLOROTHIAZIDE

*Please consult literature for dosage*

MSD MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS

# BATRILLIN
## (WOOLLEY)




* Sample available on request

**A COMBINATION OF SULPHONAMIDES WITH PENICILLIN AND CERTAIN VITAMINS OF THE "B" GROUP FOR ORAL USE**

'Batrillin' is of value in the treatment of pneumonia, urethritis, otitis media, mastoiditis, tonsillitis, sinusitis, scarlet fever, gonorrhoea and intra-uterine infections which may involve a wide range of organisms.

'Batrillin' may also be used prophylactically prior to many minor surgical operations.

| FORMULA: | | |
|---|---|---|
| | Sulphadimidine B.P. | 0·0925G |
| | Sulphamerazine B.P.C. | 0·0925G |
| | Sulphadiazine B.P. | 0·065G |
| | Nicotinamide B.P. | 10 mgms. |
| | Aneurine Hydrochloride B.P | 1·5 mgms. |
| | Penicillin B.P. | 100,000 units |

Manufactured in the laboratories of

POISON | S1 | S4

**JAMES WOOLLEY SONS & CO. LTD., VICTORIA BRIDGE, MANCHESTER, 3**

Associated with J. C. Arnfield & Sons Ltd., Stockport

# Availability of Vitamins in Yeast

Deficiencies of single factors of the Vitamin B Group do not occur. Accordingly, even if a deficiency condition appears to result from the lack of an individual factor of the group and it is considered necessary to give intensive treatment with this factor *the entire Vitamin B Complex should always be administered concurrently.*

It is, however, extremely important, in view of suggestions in recent publications, that the vehicle selected as a source of the entire B Complex does not withhold its vitamin content from the patient.

**Human experiments show that the rich, natural vitamin potency of Aluzyme is totally available to the human system.**



*Have you had your free copy of:— "The Therapeutic and Nutritional Value of Brewers' Yeast"?*

● **Aluzyme is not advertised to the public and may be prescribed on form E.C.10**

**ALUZYME**
*The NON-AUTOLYSED YEAST*
with completely available Vitamins

*Professional Samples and Prices on request from:*

**ALUZYME PRODUCTS, Park Royal, London, N.W.10**

# "IMPROVED THERAPY FOR PEPTIC ULCER"

**Extract from the American Journal of Gastroenterology (1957), 28, 439.**

"The medication investigated is known as Roter tablets . . . The dosage employed in the treatment of gastric or duodenal ulcer was 2 tablets, taken three times a day with tepid water immediately after meals . . . this therapy is applicable to ambulatory patients."

## SUMMARY

"In a series of 155 cases of peptic ulcer treated with . . . (Roter) tablets for three to six weeks, there was immediate relief of pain in 92 per cent of cases and roentgenological healing of the ulcer in 81 per cent. The average weight gain was 7.9 lbs. and occult blood disappeared from the stools in all of the six cases in which it was found.

"The benefit provided by the medication is attributed to the minute particulation of the bismuth subnitrate, produced by a special process of trituration in association with a synergistic antacid combination.

"The special features of this medication are immediate and prolonged relief of pain, correction of gastric hyperacidity, absence of side reactions, effectiveness for ambulatory patients, and early healing of the ulcer in most cases.

"There was no acid rebound in therapeutic dosage and no adverse effects were reported."

ROTER

**PACKINGS:** Tins of 40, 120, 640 and dispensing size 720 (P.T. exempt). Basic N.H.S. price: 1/- for 10 tablets.

**ROTER may be prescribed on E.C.10 forms. Literature and samples on request.**

F.A.I.R. LABORATORIES LTD TWICKENHAM · MIDDLESEX

# ST. ANDREW'S HOSPITAL

## FOR NERVOUS AND MENTAL DISORDERS

## NORTHAMPTON

*President*—THE EARL SPENCER

*Medical Superintendent*—THOMAS TENNENT, M.D., F.R.C.P., D.P.H., D.P.M.

THIS Registered Hospital is situated in 130 acres of park and pleasure grounds. Voluntary patients, who are suffering from incipient mental disorders or who wish to prevent recurrent attacks of mental trouble, temporary patients and certified patients of both sexes are received for treatment. Careful clinical, biochemical, bacteriological and pathological examinations. Private rooms with special nurses, male or female, in the Hospital or in one of the numerous villas in the grounds of the various branches, can be provided.

### WANTAGE HOUSE

This is a Reception Hospital in detached grounds with a separate entrance, to which patients can be admitted. It is equipped with all the apparatus for the complete investigation and treatment of Mental and Nervous Disorders by the most modern methods: insulin treatment is available for suitable cases. It contains special departments for Hydrotherapy by various methods, including Turkish and Russian Baths, the prolonged immersion bath, Vichy Douche, Scotch Douche, Electrical baths, Plombiere's treatment, etc. There is an Operating Theatre, a Dental Surgery, an X-ray Room, an Ultra-Violet Apparatus, and a Department for Diathermy and High-Frequency treatment. It also contains Laboratories for Biochemical, Bacteriological and Pathological Research. Psychotherapeutic treatment is employed when indicated.

### MOULTON PARK

Two miles from the main Hospital there are several branch establishments and villas situated in a park and farm of 650 acres. Milk, meat, fruit and vegetables are supplied to the Hospital from the farm, gardens and orchards of Moulton Park. Occupational Therapy is a feature of this Branch, and patients are given every facility for occupying themselves in farming, gardening and fruit growing.

### BRYN-Y-NEUADD HALL

The seaside house of St. Andrew's Hospital is beautifully situated in a park of 330 acres, at Llanfairfechan, amidst the finest scenery in North Wales. On the north-west side of the Estate a mile of sea-coast forms the boundary. Patients may visit this branch for a short seaside change or for longer periods. The Hospital has its own private bathing house on the seashore. There is trout-fishing in the park.

---

At all the branches of the Hospital there are cricket grounds, football and hockey grounds, lawn tennis courts (grass and hard courts), croquet grounds, golf courses, and bowling greens. Ladies and gentlemen have their own gardens, and facilities are provided for handicrafts, such as carpentry, etc.

For terms and further particulars apply to the Medical Superintendent: TELEPHONE No. 4354 Northampton (three lines) who can be seen in London by appointment.

---

# RIDDOSEDD TABLETS

A Compound of SODIUM-DIETHYLBARBITURATE-PHENACETIN-CODEINE The ideal HYPNOTIC, SEDATIVE, SOPORIFIC and ANALGESIC

- **RIDDOSEDD** induces a calm, natural sleep of several hours without any resulting somnolence.
- **RIDDOSEDD** has no injurious effects upon the heart, circulation, kidneys or respiration.
- **RIDDOSEDD** is timed to set in when patients awake during the early hours of the morning, thus ensuring a continuation of normal sleep.
- **RIDDOSEDD** as a soporific is 20 times greater than that of Sodium Diethylbarbiturate.
- **RIDDOSEDD** has proved to be a most reliable and best tolerated soporific and sedative for more than twenty years.

PACKED IN BOTTLES OF 20 and 100
Please write for details to:—

*Sole Manufacturers:*

## RIDDELL PRODUCTS LIMITED

RIDDELL HOUSE, 10-14 DUNBRIDGE STREET, LONDON, E.2
*Telephone: SHOreditch 7254. Telegrams: Pneumostat, Beth, London*

***BRANCH OFFICE:*** 11 Mansfield Chambers, St. Ann's Square, Manchester 2




## A practical reference manual on contraception

### *available free to all doctors*

The Report of the Royal Commission on Population (1949) states:

> *"... there is nothing inherently wrong in the use of mechanical methods of contraception... public policy should be based on acceptance of voluntary parenthood and contraception."*

These words give authoritative support to the use of conception control methods as a means of planning the size of the family.

MODERN CONTRACEPTIVE TECHNIQUE presents a concise and compact survey of methods commonly used. There are notes on methods which have medical approval, and also on others which are medically contra-indicated.

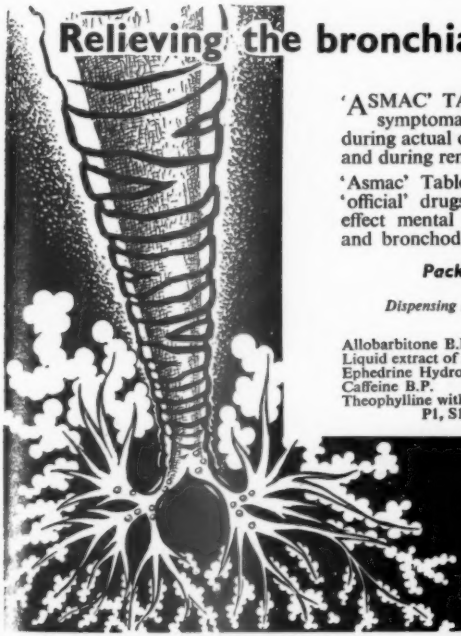
**TO GET YOUR COPY**
write "Modern Contraceptive Technique" and "Planned Families" on your letterhead and post it to the address below.




**For the use of patients**
PLANNED FAMILIES explains contraceptive techniques in non-technical terms. Any number of copies will be supplied to doctors for distribution to their patients.

**LONDON RUBBER CO. LTD., Department 308, HALL LANE, LONDON, E.4**

## Relieving the bronchial tree in asthma



'ASMAC' TABLETS are formularized to provide symptomatic relief of the bronchial tree both during actual dyspnoeic attacks of bronchial asthma, and during remissions.

'Asmac' Tablets combine in a single prescription 'official' drugs recognized for their reliability to effect mental sedation, decongestion, expectoration and bronchodilatation.

***Packs and Costs to Pharmacists:***

*Standard Tube of* 20: 3/-
*Dispensing Bottles:* 100, 12/-; 500, 52/6; 1,000, 102/6

*Formula (each tablet)*

| | | |
|---|---|---|
| Allobarbitone B.P.C. ... ... ... | 0.03 g. | (0.46 grain) |
| Liquid extract of Ipecacuanha B.P. ... | 0.02 ml. | (0.34 minim) |
| Ephedrine Hydrochloride B.P. ... ... | 0.015 g. | (0.23 grain) |
| Caffeine B.P. ... ... ... ... | 0.10 g. | (1.54 grains) |
| Theophylline with Ethylenediamine B.P. | 0.15 g. | (2.31 grains) |

P1, S1, S4. *Permissible on N.H.S. scripts.*

**Asmac**

**WANDER**

A. WANDER LIMITED, 42 Upper Grosvenor Street, Grosvenor Square, London W.1

M.372



# a great comfort during early pregnancy

## ANCOLOXIN
TABLETS TRADE MARK

**'Ancoloxin' is now well established as a real comfort to expectant mothers, in controlling pregnancy sickness.**

Meclozine hydrochloride 25 mg., plus pyridoxine hydrochloride (vitamin $B_6$) 50 mg.
Meclozine hydrochloride is given for central control of the vomiting and pyridoxine hydrochloride for basic nutrition restoration.

| | |
|---|---|
| **DOSAGE** | Two tablets at night until the condition is under control. |
| **BASIC N.H.S. PRICES** | Tubes of 10 tablets 6/4<br>Bottles of 50 tablets 26/- |

**THE BRITISH DRUG HOUSES LTD. (Medical Department) LONDON N.1** BDH




**Migraine in Wonderland**

The fantasies of altered body size and shape in *Alice in Wonderland* are like those experienced by some migraine patients.[1] Disorders of body image may be found in migraine either as an aura to an attack or as a migrainous equivalent.[2]

Lewis Carroll himself suffered from migraine[1], and it may well be that "Alice trod the paths and byways of a Wonderland well known to her creator."[3] If that is so, English literature is the richer for Mr. Carroll's migraine.[2]

Curiouser and curiouser . . .
to picture Alice's adventures (would she have had any?)
if Cafergot had been at hand
for Lewis Carroll's migraine . . .

[1]*J. nerv. ment. Dis.* (1952) 116, 346 [2]*Lancet* (1956) 1, 794
[3]*Canad. med. Ass. J.* (1955) 73, 701

**Cafergot**

BY **SANDOZ**

**aborts the attack of migraine in more than 80% of cases**




TABLETS
SUPPOSITORIES

**Sandoz House** **23 Great Castle Street** **London, W.1**

**One twentieth**
**the incidence**
**of major toxic reactions**
**encountered with**
**methylthiouracil**



# NEO-MERCAZOLE

*the anti-thyroid drug of choice*

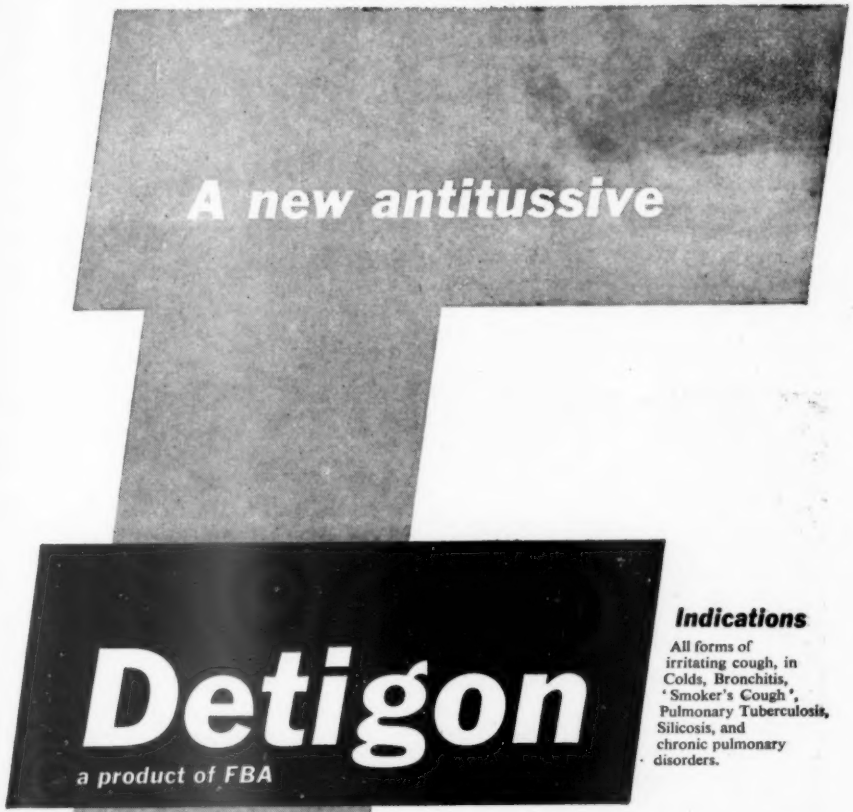
PRESENTATION

Neo-Mercazole is available as tablets, each containing 5 mg. carbimazole.

Containers of 100 and 500.

*We shall be pleased to supply further information on request*

BRITISH SCHERING LTD., 229-233 Kensington High St., London W.8. tel: Western 811




**Indications**

All forms of irritating cough, in Colds, Bronchitis, 'Smoker's Cough', Pulmonary Tuberculosis, Silicosis, and chronic pulmonary disorders.

**Packing:**
**Dropper bottles of 10ml. and 50ml.**

A safe, potent antitussive with an entirely new chemical basis and well tolerated by both adults and children.

DETIGON is free from undesirable side effects, is not habit forming or constipating.

The antitussive potency of Detigon is equal to that of codeine but without its disadvantages. A mild local anaesthetic activity renders Detigon also valuable in Tonsillectomy (post-operatively) and in diagnostic and therapeutic procedures where suppression of cough is necessary or desirable.

**Dosage**

Adults, 15-20 drops 3-4 times daily
Children, 5-15 drops according to age 3-4 times daily
Infants, up to 2 years, 5 drops 3-4 times daily.

DETIGON contains in each ml. 50 mg. of 1-o-chlorphenyl-3-dimethylamino-l-phenylpropan-l-ol-hydrochloride.

Basic N.H.S. Price 10 ml. bottle, 2/-: 50 ml. bottle, 9/4.

*Samples and literature on request.*

*Sole distributors for Farbenfabriken Bayer A.G. Leverkusen, Germany, are Levmedic Ltd., 37/41, Bedford Row, London, W.C.1, to whom all communications should be addressed.*

**NEW ANTIBIOTIC PRODUCTS FOR TOPICAL APPLICATION**

*For the treatment of the combined picture of reaction and infection, whichever is the primary element*



# Framycort

LOTION

Combined steroid-antibiotic therapy. Antibacterial, anti-inflammatory, antipruritic.

CHIEF INDICATIONS

Otitis externa
Anogenital pruritus
Seborrhoeic dermatitis
and all cases where infection complicates the eczema-dermatitis group of reactions.

| PRODUCT | FORMULA | PACK | BASIC N.H.S. COST |
|---|---|---|---|
| Framycort | framycetin sulphate 0.5% hydrocortisone acetate B.P. 0.5% | 20 ml. | 9/6 |
| Framygen | framycetin sulphate 0.5% | 15 G. | 4/- |

ALSO

# Framygen

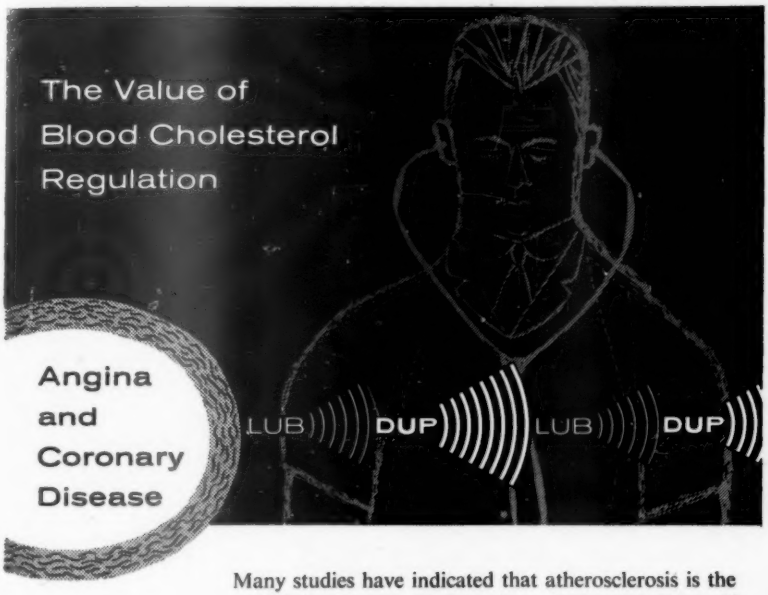
—A STRAIGHT ANTIBIOTIC CREAM

CHIEF INDICATIONS

Otitis externa
Impetigo
Sycosis barbae




GENATOSAN LIMITED, LOUGHBOROUGH, LEICESTERSHIRE




Many studies have indicated that atherosclerosis is the underlying disease process in a large percentage of cases of myocardial infarction or angina pectoris. It is also known that blood cholesterol and other lipoprotein levels are frequently high in coronary disease.

For the reduction and regulation of elevated cholesterol levels, a new practical method providing effective action without the imposition of radical dietary restrictions is now available in

# Arcofac

ARMOUR
CHOLESTEROL LOWERING
FACTOR

Arcofac is a bland palatable emulsion of Linoleic Acid with Vitamin $B_6$ and Vitamin E, which can be taken alone or mixed with most foods and beverages.

*Issued in 6 and 12 oz. bottles* *Literature on request*

**ARMOUR PHARMACEUTICAL COMPANY**
(ARMOUR CHEMICAL INDUSTRIES LTD)
**HAMPDEN PARK, EASTBOURNE, ENGLAND**
Telephone : Hampden Park 740. Telegrams : ARMOLAB, Eastbourne



*Announcing*

**SYRUP**

Trade **'V-CIL-K'** Mark

PAEDIATRIC

This new paediatric syrup of 'V-Cil-K' gives even the youngest patient convenient and decisive penicillin therapy. Each 5 cc. contains 125 mg. penicillin V potassium—the most effective oral penicillin yet developed. Peak levels are attained within 30 minutes, from a syrup so pleasantly flavoured that regular dosage is assured.

The dose is ¼ to 1 teaspoonful four times daily.

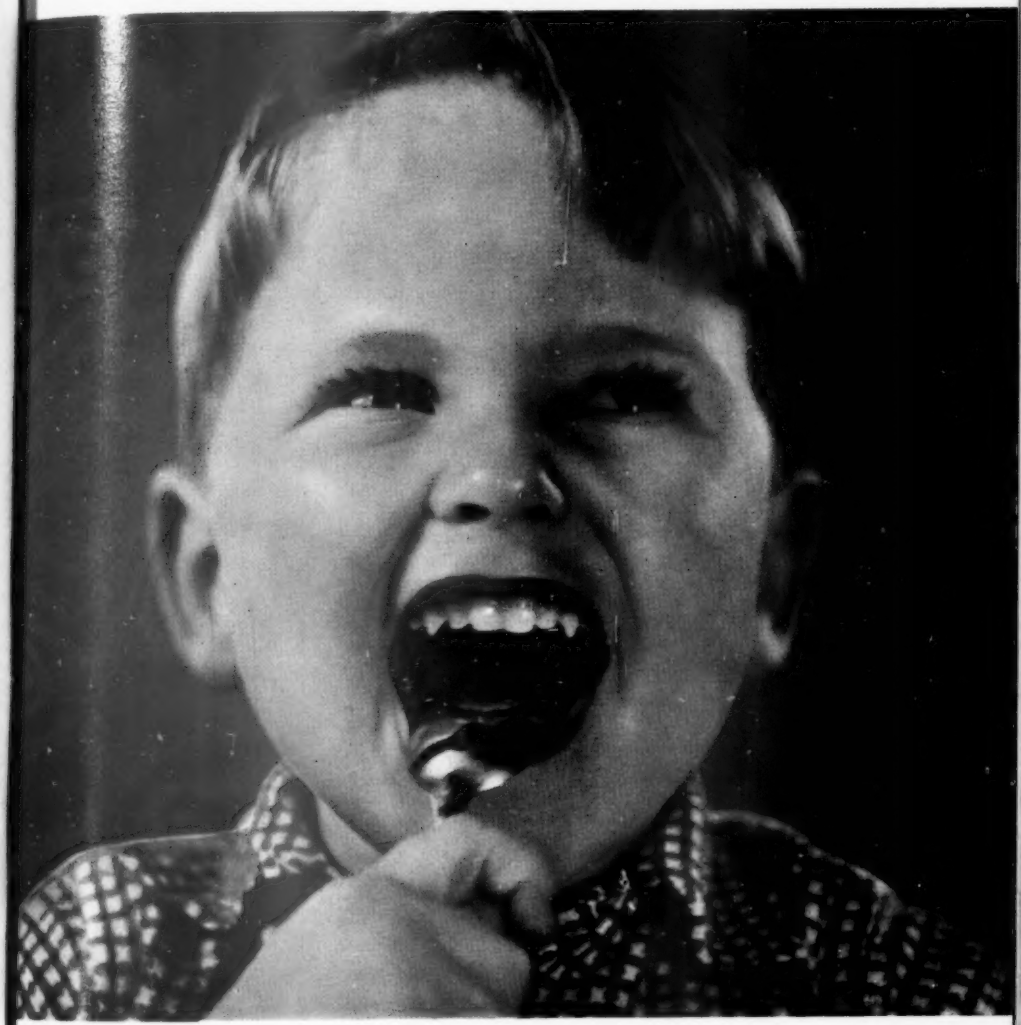
Available in bottles to make 30 cc. and 60 cc., each with a 5 cc. plastic spoon.

SYRUP
**'V-CIL-K'**
PENICILLIN V POTASSIUM

Lilly

ELI LILLY AND COMPANY LIMITED • BASINGSTOKE • ENGLAND

# He doesn't know it gives faster, higher blood levels



## But he does know it tastes good

# ACHROMYCIN* V

TETRACYCLINE WITH CITRIC ACID AND SODIUM CITRATE

*REGD. TRADEMARK

**SYRUP**
Each teaspoonful (5cc.) contains 125 mg. tetracycline.
Bottles of 2 fl. oz. and 16 fl. oz.

**PEDIATRIC DROPS AQUEOUS**
Each cc. contains 100 mg. tetracycline—approximately 5 mg. per drop.
Plastic dropper-type bottle of 10 cc.

Lederle

LEDERLE LABORATORIES DIVISION
Cyanamid OF GREAT BRITAIN LTD., London, W.C.2

CYANAMID

**Fred has had pneumonia again.** Different from last time though, he said. Four tablets a day, that was all; and none of those injections, thank goodness. His doctor is also thankful.

He knows he saves time and can rely on this simpler oral method of attaining high initial as well as sustained blood levels in adult patients with acute infections.

He prescribes **Pen-Vee-Dural** *

*Packs of 12 and 100 tablets. Each tablet contains 150,000 units benzathine penicillin plus 60 mg. penicillin V.*

* *trade mark*

Wyeth

John Wyeth & Brother Limited, Clifton House, Euston Road, London, N.W.1.

Pv.4





**UNIQUE** among oral antibiotics

With any other oral antibiotic, divided doses must be given frequently to maintain a continuous adequate effect, whatever the total daily dose decided upon. With Biotexin, since it is eliminated very slowly, increase of dose gives a substantial increase in blood level and duration of therapeutic effect. There is actually an advantage in giving fewer and larger doses at longer intervals; 1 gram once a day or 0·5 gram twice daily is usually favoured.

**PROMPT**

Biotexin promptly produces bactericidal blood levels far in excess of those achieved by other oral antibiotics

**PERSISTENT**

Biotexin maintains bactericidal concentrations in the blood longer than other oral antibiotics

# BIOTEXIN

BIOTEXIN
TRADE MARK
NOVOBIOCIN GLAXO

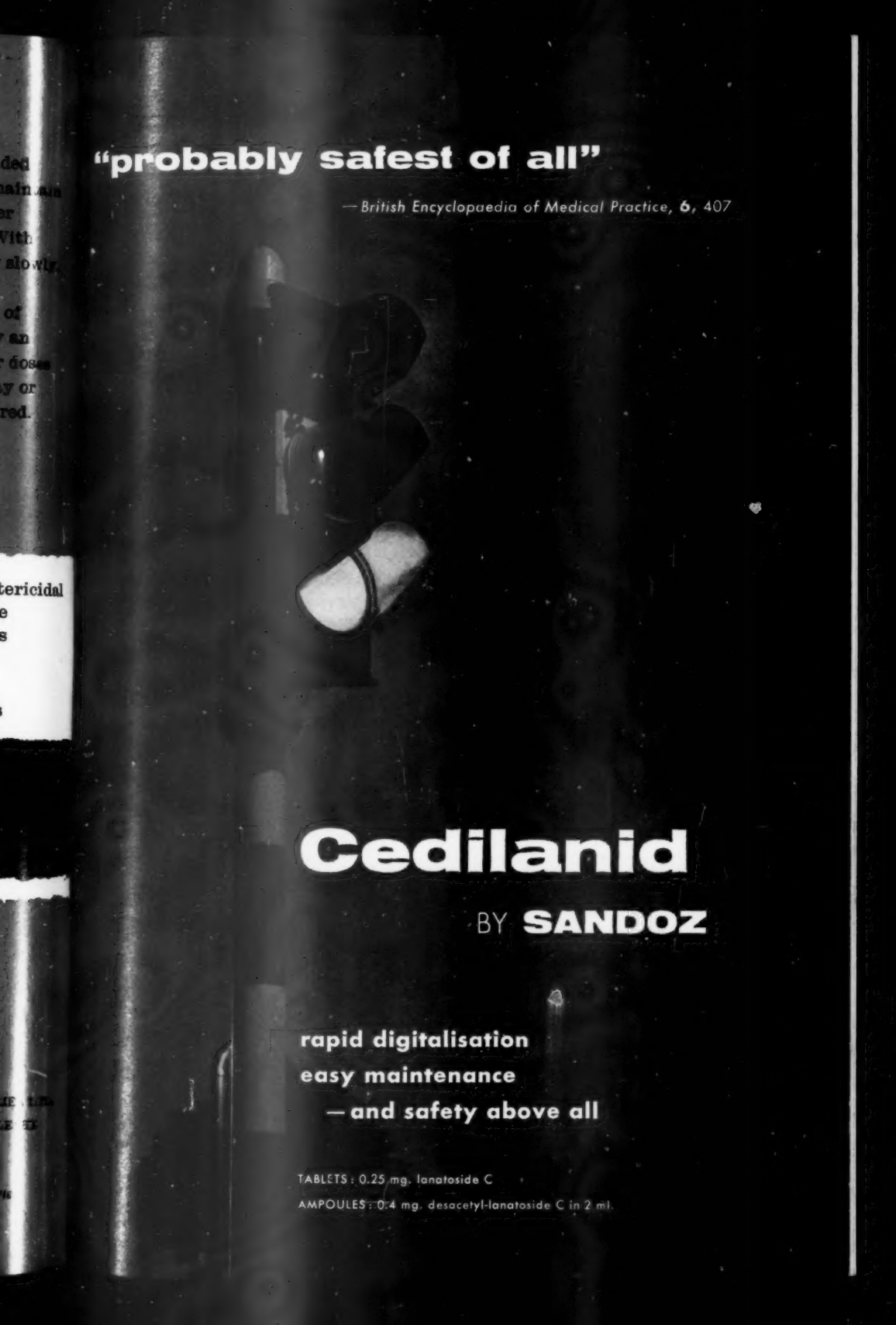
The prompt and persistent oral antibiotic in two easy-to-take forms:

*Tablets for adults, 125 mg novobiocin (as sodium salt). Bottles of 32 and 100.*

Syrup for children, 125 mg. novobiocin (as calcium salt), per 5 ml dose. Bottles 2 fl. oz. (12 doses).

**NEW**

GLAXO LABORATORIES LTD.
GREENFORD, MIDDLESEX
SYRon 2434
*Subsidiary Companies or Agents in most countries*


"probably safest of all"
— British Encyclopaedia of Medical Practice, 6, 407
Cedilanid
BY SANDOZ
rapid digitalisation
easy maintenance
— and safety above all
TABLETS : 0.25 mg. lanatoside C
AMPOULES : 0.4 mg. desacetyl-lanatoside C in 2 ml.

# Relief of
# RHEUMATIC PAINS
## with diethylamine salicylate

Algesal is the original skin-penetrating cream containing diethylamine salicylate. In 1955 a report of a clinical trial with Algesal appeared in the British Journal of Physical Medicine[1]. The report concluded:

**"This preparation is a valuable addition to our therapeutic resources for the symptomatic relief of rheumatic pains. Clinical trial of 10% diethylamine salicylate cream *(Algesal)* showed significant relief of soft tissue rheumatic pains as compared with a dummy preparation."**

Experimental work[2] has proved that diethylamine salicylate has a skin penetrative power 3 to 5 times that of other salicylates studied, and is completely non-irritating to the skin.

Over the past 5 years wide medical experience with Algesal has shown that symptomatic relief of common soft-tissue rheumatism can be achieved *without* counter-irritation, by the percutaneous route.

Algesal Balm contains the single active ingredient —10% diethylamine salicylate— in a soothing vanishing cream.

It is indicated in all the rheumatic syndromes seen in general practice: fibrositis, lumbago, osteo-arthritis, tenosynovitis, pain and stiffness after exercise.

Pads of tear-off leaflets describing special remedial exercises are available for giving to patients with lumbo-sacral strain, osteoarthritis of the knee, frozen shoulder and painful foot strain.

[1] March 1955. p.62
[2] Halpern, B., Gaudin, O., et al (1948) C. R. Soc. Biol. (Paris) **142**, 819

**Algesal**

percutaneous salicylate cream for the relief of rheumatic pain by inunction

Samples and full descriptive literature available on request to

**E.G.H. LABS. Peru Street, Salford 3, Lancs.**




# *Safety in Barbiturate Therapy*

***risk of 'accident' from overdosage virtually eliminated***

Search for a less toxic form for the administration of Barbiturates has shown that the incorporation of 'MEGIMIDE' (Bemegride), while preserving the major therapeutic actions of the barbiturates, significantly modifies their usual toxic manifestations at overdosage levels.

**'MEGOBAR'** *Trade Mark* providing safer sedation

*Tablets each containing:—*

| | |
|---|---|
| Phenobarbitone | 30 mg. |
| 'MEGIMIDE' | 3 mg. |

In bottles of 100 tablets—Basic N.H.S. Price 4/1d. plus P. Tax 1/3d.

**'PHENAGLATE'** *Trade Mark* a quick-acting, medium duration hypnotic for routine use.

*Capsules each containing:—*

| | |
|---|---|
| Quinalbarbitone sodium | 50 mg. |
| Phenobarbitone | 25 mg. |
| 'MEGIMIDE' | 7.5 mg. |

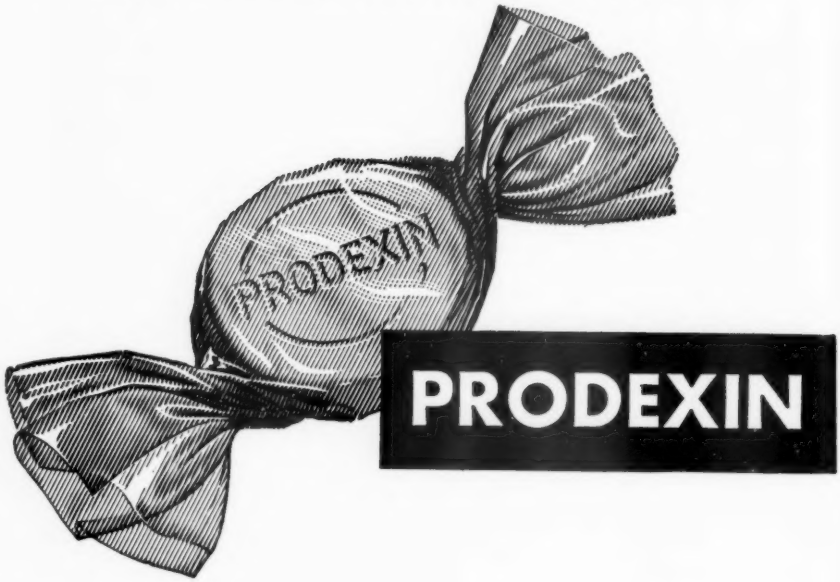
In bottles of 30 capsules—Basic N.H.S. Price 6/-d. plus P. Tax 1/9d.

*Literature and samples on request*

A Nicholas Product

**Aspro-Nicholas Ltd.** *Slough, Bucks, England*
(*Ethical Pharmaceutical Division*)

**PREDICTABLE** *ANTACID THERAPY*




1 **rapidly relieves gastric pain**
2 **safely buffers excess acid**
3 **non-alkalising**
4 **non-constipating**
5 **stable, consistent and predictable**

**Prodexin** tablets sucked regularly provide continuous buffering of gastric acid at about *p*H 4, in the face of widely differing acidities and irrespective of the rate of emptying of the stomach. Prodexin does not make the stomach alkaline and does not stimulate compensatory secretion of acid. The tablets are pleasant to take, non-gritty and non-constipating.

**PRODEXIN**
**Each Prodexin tablet contains:**
Aluminium glycinate
(dihydroxy aluminium aminoacetate).....0·9 gramme
Light magnesium carbonate..... 0·1 gramme

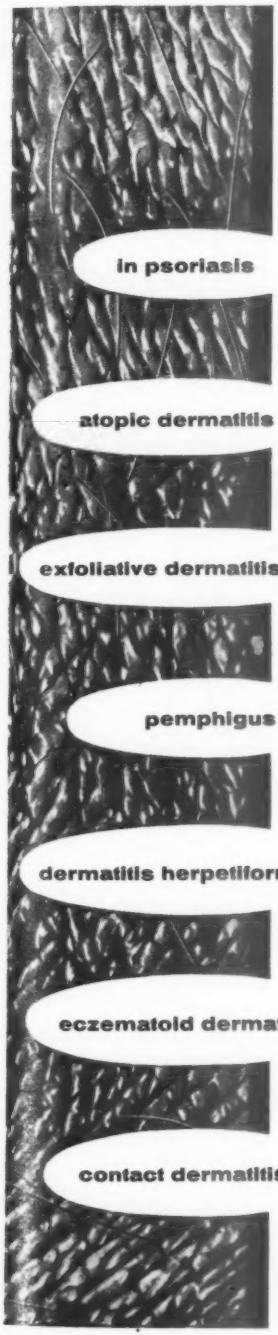
*Cartons of 30 singly wrapped tablets.*

*Dispensing packs of 240 tablets (basic N.H.S. cost 23/4d.)*




631/60/3

**C. L. BENCARD LTD.** · PARK ROYAL · LONDON · N.W.1




# Ledercort*

TRIAMCINOLONE

* REGD. TRADEMARK

## in the control of psoriasis and other dermatoses

Studies[1] confirm that LEDERCORT triamcinolone gives symptomatic relief on a substantially lower dosage than other steroids, and fewer side effects. Shelley *et al*[2]. reported that 36 of a series of 60 patients with psoriasis responded rapidly and dramatically to LEDERCORT in doses of 12 to 16 mg. daily. In some patients, the psoriasis was completely erased within 2 to 4 weeks.

[1] Rein, C. R. *et al.*, *J.A.M.A.* *165*: 14: 1821-1823 (Dec. 7) 1957.

[2] Shelley, W. B., Harun, J. S. and Pillsbury, D. M.: *J.A.M.A.* *167*: 8: 959-964 (June 21) 1958.

**Ledercort**

*Oral tablets of 2 mg. and 4 mg., scored for easy division. Bottles of 30, 100 and 500.*

**LEDERLE LABORATORIES DIVISION**

*Cyanamid OF GREAT BRITAIN LTD., London, W.C.2*

Lederle

CYANAMID

## THE VICTORIAN GOVERNESS



"Whether a governess belonged by birth to the Church, the nobility, or to the Army, her profession had never before been so exploited!"

In the Royal Academy of 1845 a picture was hung which showed the period governess seated in her schoolroom, far away from home. It was "The Poor Teacher" who suffered such harsh treatment at the hands of her insensitive employers. There was, of course, the other side of the picture portrayed by Thackeray who suffered considerably from the steady stream of incompetent governesses passing through his home.

In 1843, the G.B.I. was founded to "remedy the existing evils in Female Education, and of removing them in future, and of benefiting Governesses in general." From then onwards the status of the Governess improved, and the G.B.I. is still looking after those who, through no fault of their own, are in need of help.

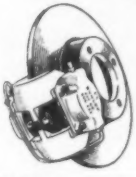
## GOVERNESSES' BENEVOLENT INSTITUTION

(*for the benefit of Governesses and private teachers*)
58 VICTORIA STREET, LONDON, S.W.1

# *And now the* JAGUAR

*mark* IX *nine*





*The latest race-proved* DUNLOP DISC BRAKE *safest, most efficient brake in the world.*

**WITH 3·8 LITRE 220 B.H.P. ENGINE, DISC BRAKES AND POWER-ASSISTED STEERING**

As an addition to the world famous Mark Eight saloon comes the more powerful Mark Nine model, amply demonstrating the success achieved by Jaguar engineers in constantly developing the characteristics which the ideal luxury car should possess. Its 3.8 litre, 220 b.h.p. engine offers phenomenal acceleration with high cruising speeds of 80/90 m.p.h. and a maximum of 115 m.p.h. Finger-light power-assisted steering ensures perfect control, whilst the unparalleled stopping-power of race-proved Dunlop Disc Brakes on all four wheels invests the Mark Nine with the highest degree of safety. As in the Mark Eight, interior furnishings are the last word in luxurious comfort.

**THE JAGUAR RANGE OF MODELS COMPRISES :—**

*The Mark Nine Saloon • The Mark Eight Saloon • The 3.4 Saloon The 2.4 Saloon • The XK150 Drophead Coupe • The XK150 Fixed Head Coupe • The XK150 Roadster*

JAGUAR CARS LIMITED · COVENTRY · *London Showrooms:* 88 PICCADILLY W.1

# Only Nulacin provides intragastric milk-alkali drip therapy for the ambulatory patient











*"In view of the ineffectiveness of most of the tableted antacids, the milk alkali tablet (Nulacin) would appear to be the antacid of choice for ambulatory therapy."*

(Medical Times 1958, **1**, 74)

**NULACIN TABLETS** have been developed so that when allowed to dissolve slowly in the mouth, they give continuous milk-alkali drip therapy and provide a treatment of peptic ulcer and other conditions associated with hyperacidity. The effectiveness of Nulacin therapy has been established by clinical work in many countries. The following are a few references to the literature:


Antacids. *The Practitioner*, January 1957, **178:** 43

Antacids in Peptic Ulcer. *The Practitioner*, January 1956, **176:** 103

Recent Advances in the Ulcerative Diseases of the Gastrointestinal Tract. *Amer. J. Gastro.*, December 1956, **26:** 665

Ambulatory Continuous Drip Method in the Treatment of Peptic Ulcer. *Amer. J. Dig. Dis.*, March 1955, **22:** 67-71

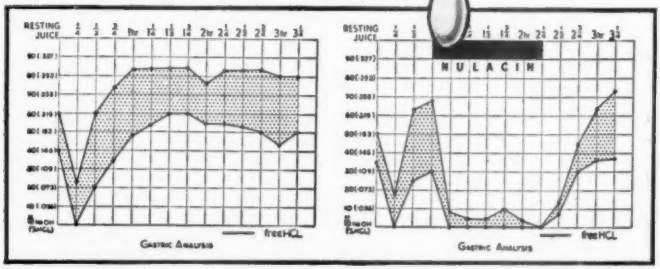
Management of Peptic Ulceration in General Practice. *Med. World*, December 1954, **81:** 591-601

Clinical Investigation into the Action of Antacids. *The Practitioner*, July 1954, **173:** 46

Further Studies on the Reduction of Gastric Acidity. *Brit. Med. J.*, 23rd January 1954, **1:** 183-184

Control of Gastric Acidity by a New Way of Antacid Administration. *J. Lab. & Clin. Med.*, 1953, **42:** 955

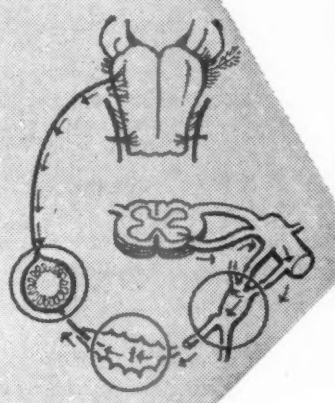
The Effect on Gastric Acidity of "Nulacin" Tablets. *Med. J. Aust.*, 28th November 1953, **2:** 823-824


Nulacin tablets have no B.P. equivalent and have been classified in categories 3 & 4 by the Joint Committee on Prescribing. The basic N.H.S. price of the 25 tablet tube is 2/-.

*Further information is available from:*
HORLICKS LTD., PHARMACEUTICAL DIVISION, SLOUGH, BUCKS

*Effective and safe treatment of Peptic Ulcer*



**Pro-Banthine**

BRAND OF PROPANTHELINE BROMIDE

Pro-Banthine is the standard anticholinergic drug which, in properly adjusted dosage, effectively suppresses gastric hypermotility, reduces the volume of gastric secretion and encourages healing of all types of peptic ulcer. By suppressing gastric motility a test dose will help to provide a clear X-ray picture for diagnosis.

**ORALLY**
Both PRO-BANTHINE (15 mg.) and PRO-BANTHINE with Phenobarbitone (15 mg. of each) are available in sugar-coated tablets in bottles of 40, 100 and 1,000 tablets.

**PARENTERALLY**
1 c.c. vials containing 30 mg. of PRO-BANTHINE as a dry, sterile powder for preparation of intramuscular or intravenous injections are available in boxes of 6 and 25 vials.

SEARLE

HIGH WYCOMBE, BUCKS.

# Publication Rules

**Copyright:** The Society holds the copyright of all matter accepted for publication in the *Proceedings*. Requests for subsequent publication elsewhere should be made to the Honorary Editors, Royal Society of Medicine . . . the copyright of all papers presented at meetings by Fellows of the Society or Members of the Sections (other than those which have been previously published) shall be deemed to be the property of the Society until a decision has been made by the Society in regard to their publication.

**Digests:** Requests for permission to make Digests from the *Proceedings* should be addressed to the Honorary Editors, Royal Society of Medicine.

**Manuscripts** should be concise and *carefully revised for press.* They must be top copies, typewritten in double spacing, with the author's name, degrees and address on the first page. A carbon copy should be retained by the author.

The text must contain references to all tables and illustrations; these should be numbered separately, tables in Roman and illustrations in Arabic numerals.

Dosages and other measurements should be given in metric units.

A key should be supplied for all abbreviations and symbols used in text and pictures.

**References:** The Harvard system should be followed, i.e. each work should be cited in the text by the author's name and date of publication, and at the end of the paper a list should be given in alphabetical order according to the authors' names. Names of journals should be abbreviated in accordance with the "World List of Scientific Periodicals", e.g.

ATKINSON, J. (1921) J. biol. Chem., 47, 134.

With the title of a book the place of publication should be given.

**Illustrations: Only the minimum number of illustrations can be accepted. They must be suitable for direct photographic reproduction; films and slides are not accepted.**

Important areas should be *lightly* marked in pencil on the *back* of the picture; the top of each picture should be indicated.

**Photographs, radiographs and photomicrographs** should be sharp black-and-white glossy prints. Photomicrographs of width 2½ in. can be reproduced actual size; magnification must be stated.

**Diagrams and graphs** should be drawn in Indian ink, on smooth white paper or board. If graph paper is used it should be feint blue-lined. Lines and curves must be boldly drawn, with lettering and numbers sufficiently large to permit of considerable reduction.

**Blocks** used for the illustration of articles in the *Proceedings* will be presented to authors shortly after each volume is concluded.

**Reprints and excerpts:** Authors may obtain these from the Society's printers, Messrs. Staples Printers Limited, 83-91, Great Titchfield Street, London, W.1. The appropriate order form will be sent with proofs of papers.

Others requiring single reprints should apply direct to the author. Alternatively, Sectional fasciculi may be purchased from:

**The Honorary Editors,**
**Royal Society of Medicine,**
**1 Wimpole Street,**
**London, W.1**



# Revelling in it!

AMAZING HOW FIT boys and girls can be at weekends and holidays! And then comes Monday with respiratory infections–bronchitis, temperatures, sometimes even pneumonia.

Get the young blighters back to school and play, as soon as possible, with S-mez. Ideal for children S-mez is the safest and best sulphonamide for routine use; swift and positive in action, palatable and potent; a tried and trusty friend, unbeaten since its discovery by I.C.I. fourteen years ago.



**S-MEZ**

Trade Mark

*is short for 'Sulphamezathine'*

Sulphadimidine B.P.

Basic N.H.S. costs: 6/7½d. for 100 x 0.5 G Tablets and 3/4d. for 100 ml. Oral suspension (0.5 G in each fluid drachm, 3.5 ml.)

ICI

IMPERIAL CHEMICAL INDUSTRIES LIMITED Pharmaceuticals Division Wilmslow Cheshire
Ph.756

## what is matter? ...and does it?



**This is matter. And it doesn't.**



**This is quite a different matter... AND IT DOES!**

No one would regard you as an out-and-out materialist if you admitted that Guinness really *does* matter. Guinness is a thoroughly natural drink brewed from hops, barley, water and yeast. Nothing is added to impair its goodness, and nothing is taken away. To say that Guinness is good for you is no less than the truth, as research eagerly carried out by men of science and medicine, and even laymen, will readily show. What's the matter with having one now?

## GUINNESS is good for you

G.E.2877.K

★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★

## HEDGES & BUTLER LTD.

*Wish you*

A Happy Christmas

*and offer you*

| | Bottle |
|---|---|
| PALE AMONTILLADO, Dry Sherry | 19/9 |
| CHÂTEAU LA ROSE CAPBERN St. Estèphe, vintage 1952 | 11/9 |
| CÔTES DE BEAUNE VILLAGES vintage 1954 | 12/8 |
| BOIZEL CHAMPAGNE, vintage 1949 | 28/- |
| 'IMPERIAL' Old Vintage Character Port | 22/3 |
| HEDGES & BUTLER'S PALE COGNAC (30 Years Old) | 60/- |

*obtainable at*

153 Regent St. London, W.1 or 22 The Arcade Bournemouth

*Telephone:*

REGent 4444 Bournemouth 4719

★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★

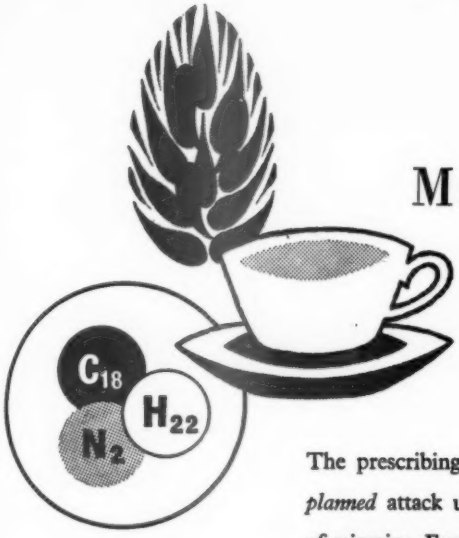
*The perfect drink for every occasion*



## JOHNNIE WALKER

Fine Old Scotch Whisky

*BORN 1820—STILL GOING STRONG*



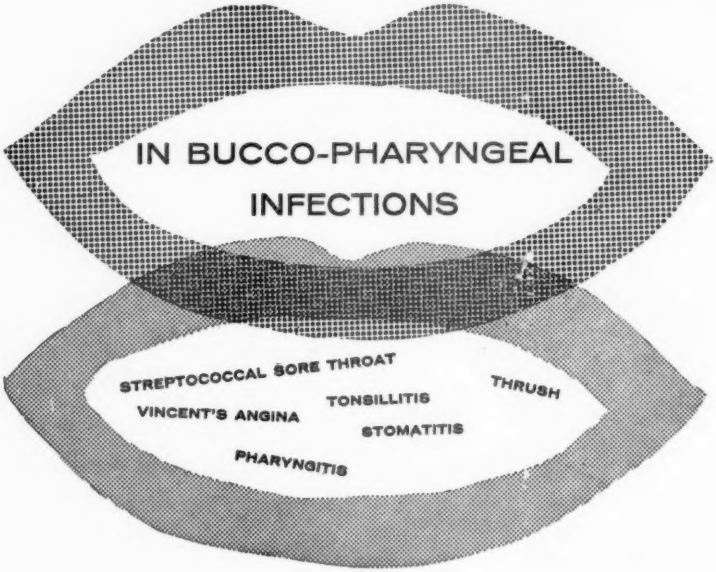

# *today's* MASTER PLAN *against migraine*

The prescribing of 'Migril' makes possible at last a *planned* attack upon the three predominant symptoms of migraine. Ergotamine is present at double strength in 'Migril' for its specific effect upon the characteristic headache and ocular disturbances. Caffeine is present too, since it acts as a synergist to ergotamine. Frequently, however, ergotamine tends to evoke nausea and vomiting on its own account and can therefore worsen these aspects of the condition. For this reason, the potent, rapidly acting anti-emetic cyclizine is also included in 'Migril'—to overcome any tendency to nausea or vomiting, whether caused by the ergotamine or by the condition itself. And so successfully does cyclizine achieve this aim that truly effective oral doses of ergotamine can today be given—by means of 'Migril'.

*Each tablet contains ergotamine tartrate* 2 *mgm.; caffeine (alkaloid)* 100 *mgm.; cyclizine hydrochloride* 50 *mgm.*
*In bottles of* 10 *and* 100

**'migril'** TRADE MARK

BURROUGHS WELLCOME & CO., LONDON
(THE WELLCOME FOUNDATION LTD.)




**DEQUADIN**

- rapidly and effectively controls the infection
- avoids the risks involved in local antibiotic therapy
- is more widely effective against oral pathogens than penicillin
- is fully active in the presence of serum
- is completely non-toxic

**DEQUADIN LOZENGES**

Each lozenge contains: *Dequadin chloride 0·25 mg. in a flavoured sucrose base.*

Available as DEQUADIN LOZENGES, in tubes of 20 lozenges.

*Dosage:* One lozenge sucked slowly every 2 or 3 hours.

**STANDARD REFERENCE CARD ON APPLICATION**

Manufactured in England by ALLEN & HANBURYS LTD LONDON E2

N58/113/H

Printed in England by Staples Printers Limited, at their Great Titchfield Street, London, establishment.

7709